

UNITED STATES DISTRICT COURT  
DISTRICT OF MASSACHUSETTS

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IN RE BIOGEN IDEC, INC. : Civil Action  
SECURITIES LITIGATION : No. 05-10400-RCL  
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**APPENDIX OF PUBLIC RECORDS CITED AS EXHIBITS  
TO MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS'  
MOTION TO DISMISS THE CONSOLIDATED CLASS ACTION COMPLAINT**

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Dated: November 15, 2006

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Dated: November 15, 2006  
Boston, Massachusetts

Respectfully submitted,

/s/ James R. Carroll

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**CERTIFICATE OF SERVICE**

I, Michael S. Hines, hereby certify that a true copy of the foregoing document filed through the ECF system will be electronically sent to the registered participants as identified on the Notice of Electronic Filing, and paper copies will be sent to those indicated as non-registered participants on November 15, 2006.

Dated: November 15, 2006

/s/ Michael S. Hines

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# **EXHIBIT 1**



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**BIOGEN IDEC AND ELAN ANNOUNCE INTENTION TO SUBMIT ANTEGREN® FOR APPROVAL FOR MULTIPLE SCLEROSIS BASED ON ONE-YEAR DATA**

**Cambridge, MA, San Diego, CA and Dublin, Ireland (February 18, 2004)** – Biogen Idec and Elan Corporation, plc today announced that they expect to submit to the U.S. Food and Drug Administration (FDA) an application for approval of ANTEGREN® (natalizumab) as a treatment for multiple sclerosis (MS). The companies expect to submit the filing mid-year 2004.

The decision to file a Biologics License Application (BLA) was made after discussions with the FDA of one-year data from the two ongoing two-year Phase III trials in MS. The companies are committed to completing the two-year trials. To protect the integrity of the trials, the companies are not disclosing the one-year data at this time.

Biogen Idec and Elan are collaborating equally on the development of natalizumab for MS, Crohn's disease, and rheumatoid arthritis.

**About the ANTEGREN MS Clinical Trials**

The AFFIRM (natalizumab safety and efficacy in relapsing-remitting MS) trial is a two-year, randomized, multi-center, placebo-controlled, double-blind study of approximately 900 patients, evaluating the ability of natalizumab to slow the progression of disability in MS and reduce the rate of clinical relapses. The SENTINEL (safety and efficacy of natalizumab in combination with AVONEX® (Interferon beta-1a)) trial is a two-year, randomized, multi-center, placebo-controlled, double-blind study of approximately 1,200 patients with relapsing-remitting MS, evaluating the effect of the combination of natalizumab and AVONEX compared to treatment with AVONEX alone in slowing the progression of disability and reducing the rate of clinical relapses. Both studies have protocols that included a one-year analysis of the data. The primary endpoints for both Phase III two-year trials in MS are based on the Expanded Disability Status Scale (EDSS) and relapse rates. The pre-specified primary endpoint of the one-year analysis was relapse rates.

### **About ANTEGREN (natalizumab)**

Natalizumab, a humanized monoclonal antibody, is the first alpha-4 antagonist in the new SAM (selective adhesion molecule) inhibitor class. The drug was designed to selectively inhibit immune cells from leaving the bloodstream and to prevent these cells from migrating into chronically inflamed tissue as occurs in a variety of inflammatory diseases. To date, approximately 2,800 patients have received natalizumab in clinical studies. In previous clinical trials, the following adverse events occurred more commonly with natalizumab when compared to placebo: headache, nausea, abdominal pain, infection, urinary tract infection, pharyngitis and rash. Serious adverse events have included infrequent hypersensitivity-like reactions.

### **About Biogen Idec**

Biogen Idec (NASDAQ: BIIB) creates new standards of care in oncology and immunology. As a global leader in the development, manufacturing, and commercialization of novel therapies, Biogen Idec transforms scientific discoveries into advances in human healthcare. For product labeling, press releases and additional information about the company, please visit <http://www.biogenidec.com>.

### **About Elan**

Elan Corporation, plc (NYSE: ELN) is focused on the discovery, development, manufacturing, selling and marketing of novel therapeutic products in neurology, severe pain and autoimmune diseases. Elan shares trade on the New York, London and Dublin Stock Exchanges. For additional information about the company, please visit <http://www.elan.com>.

### **Safe Harbor/Forward Looking Statements**

*This press release contains forward-looking statements regarding the companies' intent to file with the FDA for approval of ANTEGREN (natalizumab) and the potential of ANTEGREN as a treatment for MS. These statements are based on the companies' current beliefs and expectations. Drug development involves a high degree of risk. Factors which could cause actual results to differ materially from the companies' current expectations include the risk that unexpected concerns may arise from additional data or analysis or that regulatory authorities*

*may require additional information or further studies or that the companies may encounter other unexpected hurdles. For more detailed information on the risks and uncertainties associated with the companies' drug development and other activities, see the periodic reports of IDEC Pharmaceuticals Company, Biogen, Inc. and Elan Corporation, plc filed with the Securities and Exchange Commission. The companies assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.*

## **EXHIBIT 2**

**Cambridge, MA, San Diego, CA and Dublin, Ireland (May 25, 2004)** – Biogen Idec (NASDAQ: BIIB) and Elan Corporation, plc (NYSE: ELN) announced today that they have submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for the approval of ANTEGREN® (natalizumab) for the treatment of multiple sclerosis (MS).

The submission includes one-year data from two ongoing Phase III trials. The companies are committed to completing these two-year trials. In order to protect the integrity of the trials, the companies are not disclosing the one-year data at this time.

"Based on the one-year analysis from our Phase III studies, which include more than 2,100 patients, we believe that natalizumab has the potential to become an important new therapy for MS," said Burt Adelman, MD, executive vice president, Development, Biogen Idec. "Natalizumab's novel mechanism of action represents an innovative approach to treating MS."

"This submission represents a significant milestone for Elan and Biogen Idec and demonstrates our continued commitment to providing a new treatment option for the more than one million patients experiencing the debilitating effects of MS," said Lars Ekman, MD, executive vice president and president, Research & Development, Elan. "We look forward to working with the FDA throughout the review process to make natalizumab available to patients who may be in need."

MS is a chronic disease of the central nervous system that affects approximately 400,000 people in North America and approximately one million people worldwide. It is a disease that affects more women than men, with onset typically between 20 and 40 years of age. Symptoms of MS may include vision problems, loss of balance, numbness, difficulty walking and paralysis.

#### **About the MS Clinical Trials for ANTEGREN**

The AFFIRM (natalizumab safety and efficacy in relapsing-remitting MS) trial is a two-year, randomized, multi-center, placebo-controlled, double-blind study of approximately 900 patients, evaluating the ability of natalizumab to slow the progression of disability in MS and reduce the rate of clinical relapses. The SENTINEL (safety and efficacy of natalizumab in combination with AVONEX® (Interferon beta-1a)) trial is a two-year, randomized, multi-center, placebo-controlled, double-blind study of approximately 1,200 patients with relapsing-remitting MS, evaluating the effect of the combination of natalizumab and AVONEX compared to treatment with AVONEX alone in slowing the progression of disability and reducing the rate of clinical relapses. Both study protocols provided for a one-year analysis of the data. The primary endpoints for both Phase III two-year trials in MS are based on the Expanded Disability Status Scale (EDSS) and relapse rate. The pre-specified primary endpoint of the one-year analysis was relapse rate.

#### **About ANTEGREN (natalizumab)**

Natalizumab, a humanized monoclonal antibody, is the first alpha-4 antagonist in the new selective adhesion molecule (SAM) inhibitor class. The drug is designed to inhibit the migration of immune cells into chronically inflamed tissue where they may cause or maintain inflammation. To date, approximately 2,800 patients have received natalizumab in clinical trials, and the safety profile continues to support further development. In placebo-controlled trials to date, in both Crohn's disease (CD) and MS, the most commonly reported adverse events in either group were headache, fatigue and nasopharyngitis.

Biogen Idec and Elan are collaborating equally on the development of natalizumab in MS, CD, and rheumatoid arthritis (RA). The companies intend to submit an application for drug approval in Europe for MS by the end of the second quarter of 2004.

#### **About Biogen Idec**

Biogen Idec creates new standards of care in oncology and immunology. As a global leader in the development, manufacturing, and commercialization of novel therapies, Biogen Idec transforms scientific discoveries into advances in human healthcare. For product labeling, press releases and additional information about the company, please visit [www.biogenidec.com](http://www.biogenidec.com).

#### **About Elan**

Elan Corporation, plc is a neuroscience-based biotechnology company that is focused on discovering,

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## **EXHIBIT 3**

**FDA Designates ANTEGREN® Biologics License Application for Priority Review as a Treatment for Multiple Sclerosis**

***Application Under Accelerated Approval Guidelines***

**Cambridge, MA, San Diego, CA and Dublin, Ireland - June 28, 2004** - Biogen Idec and Elan Corporation, plc announced today that the Biologics License Application (BLA) for ANTEGREN® (natalizumab) has been designated for Priority Review and Accelerated Approval by the U.S. Food and Drug Administration (FDA) for the treatment of multiple sclerosis (MS). The next step in the process is action by the FDA on formal acceptance of the application, which occurs within 60 days of submission.

The FDA grants Priority Review status to products that are considered to be potentially significant therapeutic advancements over existing therapies that address an unmet medical need. Based on the FDA's designation of Priority Review for natalizumab in MS, the companies anticipate action by the Agency approximately six months from the submission date, rather than 10 months for a standard review. On May 25, 2004, the companies announced they had previously submitted the BLA for the approval of natalizumab for MS.

"We are pleased that the FDA has designated natalizumab for Priority Review," said Burt Adelman, MD, executive vice president, Development, Biogen Idec. "We look forward to continuing to work with the FDA throughout the review process to provide this potential new therapeutic to patients with MS."

"The Priority Review designation underscores the significant unmet medical need in the area of MS," said Lars Ekman, MD, executive vice president and president, Research & Development, Elan. "We believe natalizumab will offer a new approach to treating MS and will bring hope to patients living with this disease."

The BLA for natalizumab is being evaluated by the FDA under Accelerated Approval guidelines. This review will be based on one-year data from two ongoing Phase III trials. The companies are committed to completing these two-year trials. In order to protect the integrity of the trials, the companies are not disclosing the one-year data at this time.

MS is a chronic disease of the central nervous system that affects approximately 400,000 people in North America and approximately one million people worldwide. It is a disease that affects more women than men, with onset typically between 20 and 40 years of age. Symptoms of MS may include vision problems, loss of balance, numbness, difficulty walking and paralysis.

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**About Elan**

Elan Corporation, plc (NYSE: ELN) is a neuroscience-based biotechnology company that is focused on discovering, developing, manufacturing and marketing advanced therapies in neurology, autoimmune diseases, and severe pain. Elan shares trade on the New York, London and Dublin Stock Exchanges. For additional information about the company, please visit <http://www.elan.com>.



*This press release contains forward-looking statements regarding the approval of ANTEGREN (natalizumab) and the potential of natalizumab as a treatment for MS. These statements are based on the companies' current beliefs and expectation. Drug development involves a high degree of risk. Factors which could cause actual results to differ materially from the companies' current expectations include: the risk that unexpected concerns may arise from additional data or analysis, that regulatory authorities may require additional information, further studies, or may fail to approve the drug, or that the companies may encounter other unexpected hurdles. For more detailed information on the risks and uncertainties associated with the companies' drug development and other activities, see the periodic reports of Biogen Idec Inc. and Elan Corporation, plc filed with the Securities and Exchange Commission. The companies assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.*

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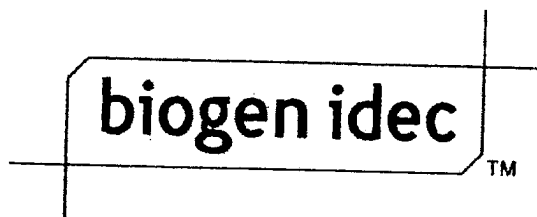
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**FDA GRANTS ACCELERATED APPROVAL OF TYSABRI® FORMERLY  
ANTEGREN®, FOR THE TREATMENT OF MULTIPLE SCLEROSIS**

**Approval of TYSABRI Marks A Major Advancement in the Treatment of MS  
Phase III Trials at One Year Demonstrate New Level of Efficacy – 66% Reduction in Rate  
of Relapses Seen in AFFIRM Monotherapy Trial**

Cambridge, MA; San Diego, CA; Dublin, Ireland – November 23, 2004 – Biogen Idec (NASDAQ: BIIB) and Elan Corporation, plc (NYSE: ELN) announced today that the U.S. Food and Drug Administration (FDA) has approved TYSABRI® (natalizumab), formerly referred to as ANTEGREN®, as treatment for relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical relapses. FDA granted Accelerated Approval for TYSABRI following Priority Review based on one-year data from two Phase III studies, the AFFIRM monotherapy trial and the SENTINEL add-on trial with AVONEX® (Interferon beta-1a).

TYSABRI, the first humanized monoclonal antibody approved for the treatment of MS, inhibits adhesion molecules on the surface of immune cells. Research suggests TYSABRI works by preventing immune cells from migrating from the bloodstream into the brain where they can cause inflammation and potentially damage nerve fibers and their insulation.

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“TYSABRI is a powerful and innovative therapy that offers new hope for hundreds of thousands of people living with MS,” said James C. Mullen, chief executive officer, Biogen Idec. “We believe TYSABRI will revolutionize the treatment of MS and become the leading choice for patients and physicians.”

“TYSABRI is a significant breakthrough for patients with MS,” said Kelly Martin, president and chief executive officer, Elan. “The approval of TYSABRI, with its unique mechanism of action and new level of efficacy, has the potential to make a genuine difference in the lives of patients and families who struggle with the debilitating effects of this disease.”

**Results of the AFFIRM Monotherapy Trial**

AFFIRM is a two-year, randomized, multi-center, placebo-controlled, double-blind study of 942 patients conducted in 99 sites worldwide, in which patients were randomized to receive either a fixed 300 mg IV infusion dose of TYSABRI (n=627) or placebo (n=315) every four weeks. TYSABRI reduced the rate of clinical relapses by 66 percent relative to placebo ( $p<0.001$ ), the primary endpoint at one-year. The annualized relapse rate was 0.25 for TYSABRI-treated patients versus 0.74 for placebo-treated patients.

AFFIRM also met all one-year secondary endpoints, including MRI measures. In the TYSABRI-treated group, 60 percent of patients developed no new or newly enlarging T2 hyperintense lesions compared to 22 percent of placebo-treated patients ( $p<0.001$ ). On the one-year MRI scan, 96 percent of TYSABRI-treated patients had no gadolinium enhancing lesions compared to 68 percent of placebo-treated patients ( $p<0.001$ ). The proportion of patients who remained relapse free was 76 percent in the TYSABRI-treated group compared to 53 percent in the placebo-treated group ( $p<0.001$ ).

**Results of SENTINEL Add-on Study**

Approval was also based on the results of another Phase III clinical trial, SENTINEL. SENTINEL is a two-year, randomized, multi-center, placebo-controlled, double-blind study of 1,171 AVONEX-treated patients in 123 clinical trial sites worldwide.

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In the SENTINEL trial, AVONEX-treated patients who continued to experience disease activity were randomized to add TYSABRI (n=589) or placebo (n=582) to their standard regimen.

SENTINEL achieved its one-year primary endpoint. The addition of TYSABRI to AVONEX resulted in a 54 percent reduction in the rate of clinical relapses over the effect of AVONEX alone ( $p<0.001$ ). The annualized relapse rate was 0.36 for patients receiving TYSABRI when added to AVONEX versus 0.78 with AVONEX plus placebo.

SENTINEL also met all secondary endpoints, including MRI measures. In the group treated with TYSABRI plus AVONEX, 67 percent of patients developed no new or newly enlarging T2 hyperintense lesions compared to 40 percent in the AVONEX plus placebo group ( $p<0.001$ ). On the one-year MRI scan, 96 percent of TYSABRI plus AVONEX-treated patients had no gadolinium-enhancing lesions compared to 76 percent of AVONEX plus placebo-treated patients ( $p<0.001$ ). The proportion of patients who remained relapse-free was 67 percent in the TYSABRI plus AVONEX-treated group compared to 46 percent in the AVONEX plus placebo-treated group ( $p<0.001$ ).

"I believe TYSABRI will be an important therapeutic advance for patients with relapsing MS," said Richard Rudick, MD, lead investigator of the SENTINEL trial and director, Mellen Center for Multiple Sclerosis, Cleveland Clinic Foundation. "Patients who have discontinued therapy, are newly diagnosed with MS, or have persistent active disease despite being on a current therapy will benefit from TYSABRI."

#### **Safety**

Common adverse events associated with TYSABRI include headache, fatigue, urinary tract infection, depression, lower respiratory tract infection, joint pain and abdominal discomfort. The rate of infection in both studies was approximately one per patient-year in both TYSABRI-treated patients and placebo-treated patients.

-MORE-

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Serious infections occurred in 1.3 percent of placebo-treated patients and 2.1 percent of TYSABRI-treated patients. Serious infections included bacterial infections such as pneumonia and urinary tract infection, which responded appropriately to antibiotics. TYSABRI has been associated with hypersensitivity reactions, including serious systemic reactions, which occurred at an incidence of less than 1 percent of patients.

**Immunogenicity**

All biologics have the potential to induce patient antibodies. Analysis of the one-year Phase III MS trials indicate a low level of immunogenicity associated with TYSABRI. Patients were tested for antibodies every 12 weeks in the AFFIRM and SENTINEL trials. Antibodies were detected in approximately 10 percent of patients at least once during treatment, with 6 percent of patients remaining persistently positive. Persistently positive antibodies were associated with a substantial decrease in efficacy and an increase in certain infusion-related adverse events. Almost all patients who tested positive for antibodies did so within the first 12 weeks of treatment.

**Two-year Results**

AFFIRM and SENTINEL are two-year trials. Two-year results are anticipated beginning in the first half of 2005. Patients who complete these trials are eligible for enrollment in a long-term safety extension study.

“The MS community is pleased that the FDA approval of TYSABRI provides an additional treatment option for people with relapsing forms of MS. There are many people living with MS who may benefit from this different treatment approach,” said Stephen C. Reingold, PhD, vice president for research, the National MS Society.

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**About TYSABRI**

Biogen Idec and Elan are collaborating equally on the development of TYSABRI in MS, Crohn's disease (CD), and rheumatoid arthritis (RA). In September 2004, a Marketing Authorisation Application (MAA) for CD was filed with the EMEA based on Phase III studies, and another Phase III induction trial for CD is ongoing. A Phase II trial is also underway to evaluate TYSABRI in RA. To date, more than 2,800 patients have received TYSABRI in clinical trials.

Information about TYSABRI, including prescribing information, and its comprehensive support services, will be available through a single toll-free number (1-800-456-2255), and via [www.TYSABRI.com](http://www.TYSABRI.com).

**About Multiple Sclerosis**

MS is a chronic disease of the central nervous system that affects approximately 400,000 people in North America and more than one million people worldwide. It is a disease that affects more women than men, with onset typically occurring between 20 and 40 years of age. Symptoms of MS may include vision problems, loss of balance, numbness, difficulty walking and paralysis.

**Webcast**

The companies will host a joint webcast for the investment community tomorrow at 8:00 a.m. EST, 1:00 p.m. GMT, which can be accessed through the companies' websites. At the conclusion of this call, Elan will have a separate conference call to address any company-specific questions at 9:15 a.m. EST, 2:15 p.m. GMT, which can be accessed through the company website.

**About Biogen Idec**

Biogen Idec creates new standards of care in oncology and immunology. As a global leader in the development, manufacturing, and commercialization of novel therapies, Biogen Idec transforms scientific discoveries into advances in human healthcare. For product labeling, press releases and additional information about the company, please visit <http://www.biogenidec.com>.

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#### **About Elan**

Elan Corporation, plc is a neuroscience-based biotechnology company. We are committed to making a difference in the lives of patients and their families by dedicating ourselves to bringing innovations in science to fill significant unmet medical needs that continue to exist around the world. Elan shares trade on the New York, London and Dublin Stock Exchanges. For additional information about the company, please visit <http://www.elan.com>.

#### **Safe Harbor/Forward Looking Statements**

*This press release contains forward-looking statements regarding the potential for TYSABRI. These statements are based on the companies' current beliefs and expectations, and are subject to risks and uncertainties that could cause actual results to differ materially. There is no assurance, for example, that all experiences with TYSABRI will be the same or that TYSABRI will not be affected by unexpected new data or technical issues or by intellectual property disputes. The potential for TYSABRI may also be influenced by reimbursement and pricing decisions, the impact of competitive products, the pace of market acceptance, and any material issues, delays or failures related to its manufacturing and supply. For more detailed information on the risks and uncertainties associated with TYSABRI and the companies' drug development and other activities, see the periodic and other reports of Biogen Idec Inc. and Elan Corporation, plc filed with the Securities and Exchange Commission. The companies assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.*

## ## ##



## **EXHIBIT 5**

The Biogen Idec logo consists of the words "biogen ideo" in a lowercase, sans-serif font. The text is enclosed within a rectangular border that has a small notch on the right side. The logo is positioned at the top of the page, with a horizontal line extending to the right from the top of the border.

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**FOR IMMEDIATE RELEASE**

**BIOGEN IDEC CHIEF OPERATING OFFICER WILLIAM ROHN TO RETIRE**

**Cambridge, MA, and San Diego, CA (November 29, 2004)** - Biogen Idec (NASDAQ: BIIB) today announced that Chief Operating Officer (COO) William R. Rohn will retire from the company effective January 31, 2005. To ensure a smooth transition, Mr. Rohn's responsibilities as COO will be assumed by James C. Mullen, Biogen Idec's Chief Executive Officer, and other members of the senior management team, starting November 30, 2004.

William H. Rastetter, Ph.D., Biogen Idec's Executive Chairman, said, "Through his vision, commitment, and strong leadership over more than a decade, Bill Rohn helped transform IDEC Pharmaceuticals Corporation from a small research organization into a very successful biotechnology company. Bill then played an instrumental role in the formation of Biogen Idec, a global biotechnology leader. We thank him for his countless contributions. He has been a great colleague and will be missed."

-MORE-

*Page 2 Biogen Idec Chief Operating Officer William Rohn to Retire*

“My eleven years at the company have been unbelievably gratifying,” said Mr. Rohn. “I’ve had the great fortune to be part of a talented team that has developed and commercialized landmark therapies in both cancer and multiple sclerosis. As a professional in the pharmaceutical industry, it doesn’t get better than that.”

Prior to the merger of IDEC Pharmaceuticals Corporation and Biogen, Inc., Mr. Rohn was President and Chief Operating Officer of IDEC Pharmaceuticals Corporation. He joined IDEC Pharmaceuticals Corporation in August 1993 as Senior Vice President, Commercial and Corporate Development. Following his departure from the company, Mr. Rohn will focus his efforts on philanthropic endeavors, community service in the San Diego, CA area, and corporate board work with early-stage biotechnology companies. Mr. Rohn is currently on the Board of Directors of both Pharmacyclics, Inc. and Cerus Corporation.

**About Biogen Idec**

Biogen Idec creates new standards of care in oncology and immunology. As a global leader in the development, manufacturing, and commercialization of novel therapies, Biogen Idec transforms scientific discoveries into advances in human healthcare. For product labeling, press releases and additional information about the company, please visit [www.biogenidec.com](http://www.biogenidec.com).

## ## ##

## **EXHIBIT 6**

## **BIOGEN IDEC AND ELAN ANNOUNCE VOLUNTARY SUSPENSION OF TYSABRI®**

**Cambridge, MA and Dublin, Ireland (February 28, 2005)** -- Biogen Idec (NASDAQ: BIIB) and Elan Corporation, plc (NYSE: ELN) announced today a voluntary suspension in the marketing of TYSABRI® (natalizumab), a treatment for multiple sclerosis (MS). The companies are suspending supply of TYSABRI from commercial distribution and physicians should suspend dosing of TYSABRI until further notification. In addition, the companies have suspended dosing in all clinical trials.

This decision is based on very recent reports of two serious adverse events that have occurred in patients treated with TYSABRI in combination with AVONEX® (Interferon beta-1a) in clinical trials. These events involve one fatal, confirmed case and one suspected case of progressive multifocal leukoencephalopathy (PML), a rare and frequently fatal, demyelinating disease of the central nervous system. Both patients received more than two years of TYSABRI therapy in combination with AVONEX.

The companies' actions have been taken in consultation with U.S. Food and Drug Administration (FDA). Worldwide regulatory agencies are being kept informed.

The companies will work with clinical investigators to evaluate TYSABRI-treated patients and will consult with leading experts to better understand the possible risk of PML. The outcome of these evaluations will be used to determine possible re-initiation of dosing in clinical trials and future commercial availability.

"Our ongoing commitment to MS patients has led us to take these steps," said Burt Adelman, MD, executive vice president, Development, Biogen Idec. "Because we believe in the promising therapeutic benefit of TYSABRI, we are working to evaluate this situation thoroughly and expeditiously. While we work through this matter, we must place patient safety above all other considerations."

"We are working with leading experts and regulatory agencies to responsibly investigate these events and to develop the appropriate path forward," said Lars Ekman, MD, executive vice president and president, Research and Development, Elan. "Our primary concern is for the safety of patients."

In total, approximately 3,000 patients have been treated with TYSABRI in clinical trials of MS, Crohn's disease, and rheumatoid arthritis. To date, the companies have received no reports of PML in MS patients receiving TYSABRI monotherapy or in patients with Crohn's disease or rheumatoid arthritis in TYSABRI clinical trials. Biogen Idec has received no reports of PML in patients treated with AVONEX alone, a product that has been on the market since 1996.

A copy of the Dear Healthcare Professional Letter regarding this matter is available at [www.tysabri.com](http://www.tysabri.com) and the companies' corporate websites. Patients and physicians with questions should call 1-888-489-7227.

Biogen Idec will host a webcast for the media and the investment community at 10:00 a.m. EST today. Elan will also host a webcast at 11:30 a.m. EST today. These webcasts can be accessed through the investor relations' sections of the companies' websites.

### **About Biogen Idec**

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### **About Elan**

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### **Safe Harbor/Forward Looking Statements**

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*Exchange Commission. The companies assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.*

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## **EXHIBIT 7**

## **ELAN AND BIOGEN IDEC ANNOUNCE TYSABRI® UPDATE**

**Dublin, Ireland and Cambridge, MA - March 30, 2005** – Elan Corporation, plc (NYSE: ELN) and Biogen Idec (NASDAQ: BIIB) announced today that their ongoing safety evaluation of TYSABRI® (natalizumab) has led to a previously diagnosed case of malignant astrocytoma being reassessed as progressive multifocal leukoencephalopathy (PML), in a patient in an open label Crohn's disease clinical trial.

In light of the two previously reported cases of PML in multiple sclerosis clinical trials, Elan and Biogen Idec initiated an additional comprehensive safety evaluation of TYSABRI clinical trial patients. In the course of this safety review, the companies identified a case warranting reassessment in an open label Crohn's disease clinical trial. In July 2003, the case was reported by a clinical trial investigator as malignant astrocytoma. This diagnosis was confirmed at the time by histopathology. The patient died in December 2003.

As part of this ongoing safety review, the companies, in agreement with the clinical trial investigator, reassessed the case. Following this additional evaluation, the diagnosis is being reassessed as PML. The patient had received 8 doses of TYSABRI over an 18 month period and prior medication history included multiple courses of immunosuppressant agents.

Elan and Biogen Idec's comprehensive safety evaluation concerning TYSABRI and any possible link to PML is ongoing. The companies are reviewing clinical trial data, working with investigators to evaluate the approximately 3,000 patients in multiple sclerosis, Crohn's disease, and rheumatoid arthritis trials, and working with PML and neurology experts. The results of this safety evaluation will be discussed with regulatory agencies to determine possible re-initiation of dosing in clinical trials and future commercial availability.

On February 28, 2005, the companies announced that they had suspended marketing of TYSABRI in multiple sclerosis and dosing in all clinical trials based on two previously reported cases of PML, a rare and frequently fatal, demyelinating disease of the central nervous system.

### **About Elan**

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### **Safe Harbor/Forward Looking Statements**

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### **For More Information Contact:**

#### **MEDIA CONTACT:**

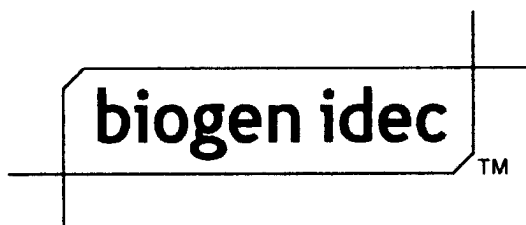
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## **EXHIBIT 8**



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**BIOGEN IDEC AND ELAN ANNOUNCE TYSABRI® SAFETY EVALUATION  
UPDATE**

**Cambridge, MA and Dublin, Ireland – August 9, 2005** – Biogen Idec (NASDAQ: BIIB) and Elan Corporation, plc (NYSE: ELN) announced today that findings from their safety evaluation of TYSABRI® (natalizumab) in patients with multiple sclerosis (MS) resulted in no new confirmed cases of progressive multifocal leukoencephalopathy (PML). The companies have previously reported three confirmed cases of PML, two of which were fatal. The ongoing safety evaluation in Crohn's disease and rheumatoid arthritis is on track to be completed by the end of the summer. The companies anticipate making submissions to regulatory authorities in early fall of 2005. The companies are taking preliminary steps to restart clinical trials in MS.

More than 2,000 MS patients from clinical trials were eligible for the safety evaluation. To date, 91% of these MS patients participated in the safety evaluation. The remaining 9% of patients did not participate in the safety review. A total of 99% of patients participating in the evaluation visited their treating physician and had a neurological exam. In addition, 98% of participants had an MRI exam. The safety evaluation also included the review of any reports of potential PML in patients receiving TYSABRI in the commercial setting.

"Our ongoing TYSABRI safety evaluation is a rigorous medical and scientific undertaking that has been led by some of the world's leading experts in neurology and neuroradiology," said Whaijen Soo, MD, PhD, senior vice president, Medical Research, Biogen Idec. "Given the high unmet medical need in MS and the therapeutic benefit we have seen with TYSABRI, we are encouraged by these safety findings."

-MORE-

*Page 2 Biogen Idec and Elan Announce TYSABRI® Safety Evaluation Update*

“The findings announced today are an important milestone in understanding the appropriate benefit-risk profile for TYSABRI. Patient safety remains our top priority. We are committed to finalizing the safety evaluation for Crohn’s disease and rheumatoid arthritis, which is progressing well and on track to be completed by the end of the summer. We look forward to working with regulatory authorities to determine the path forward for TYSABRI,” said Lars Ekman, MD, PhD, executive vice president and president, Research and Development, Elan.

On February 28, 2005, Biogen Idec and Elan announced that they voluntarily suspended TYSABRI from the U.S. market and all ongoing clinical trials based on reports of PML, a rare and potentially fatal, demyelinating disease of the central nervous system. Biogen Idec and Elan’s comprehensive safety evaluation concerning TYSABRI and any possible link to PML is ongoing. The results of this safety evaluation will be discussed with regulatory agencies to determine the appropriate path forward for TYSABRI.

Biogen Idec and Elan will host a webcast for the media and investment community at 8:30 a.m. EST today to discuss the TYSABRI safety evaluation update. This webcast can be accessed through the investor relations’ sections of the companies’ websites.

**About Biogen Idec**

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**Safe Harbor/ Forward Looking Statements**

*This press release contains forward-looking statements regarding the potential, regulatory path forward, re-start of MS clinical trials and safety evaluation of TYSABRI. The potential, regulatory path forward and re-start of clinical trials for TYSABRI are subject to a number of risks and uncertainties. Factors which could cause actual results to differ materially from the companies current expectations include the risk that concerns may arise from additional data or analysis, including the ongoing safety evaluation, or that the companies may encounter other unexpected delays or hurdles. There is also no assurance that the companies will be able to gain*

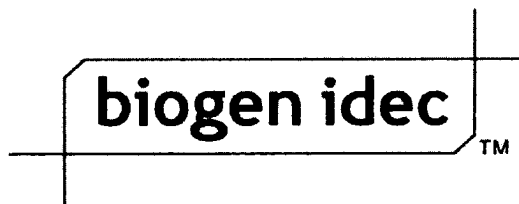
-MORE-

*Page 3 Biogen Idec and Elan Announce TYSABRI® Safety Evaluation Update*

*sufficient information to fully understand the risks associated with TYSABRI or that the companies will be able to resume marketing and sales of TYSABRI. The completion of the safety evaluation is subject to a number of risks and uncertainties, including the difficulty of analyzing complex data and results and unanticipated logistical hurdles. Drug development and commercialization involves a high degree of risk. For more detailed information on the risks and uncertainties associated with the companies' drug development and other activities, see the periodic reports that Biogen Idec and Elan have filed with the Securities and Exchange Commission. The companies assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.*

*# # #*

## **EXHIBIT 9**



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**ELAN AND BIOGEN IDEC ANNOUNCE TYSABRI<sup>®</sup> SAFETY EVALUATION  
FINDINGS IN CROHN'S DISEASE AND RHEUMATOID ARTHRITIS PATIENTS**

***TYSABRI Safety Evaluation Complete; No New Confirmed Cases of PML***

**Dublin, Ireland and Cambridge, MA ----- October 17, 2005** – Elan Corporation, plc (NYSE: ELN) and Biogen Idec (NASDAQ: BIIB) announced today that findings from their safety evaluation of TYSABRI<sup>®</sup> (natalizumab) in patients with Crohn's disease (CD) and rheumatoid arthritis (RA) resulted in no new confirmed cases of progressive multifocal leukoencephalopathy (PML). The companies have previously reported that findings from their safety evaluation of TYSABRI in patients with multiple sclerosis (MS) resulted in no new confirmed cases of PML. Three confirmed cases of PML were previously reported, two of which were fatal. The TYSABRI safety evaluation is now complete.

On September 26, 2005 the companies announced that they submitted a supplemental Biologics License Application for TYSABRI to the U.S. Food and Drug Administration (FDA) for the treatment of MS. The companies also recently submitted a similar data package to the European Medicines Agency.

More than 1,500 CD and RA patients from clinical trials were eligible for the safety evaluation. A total of 88% of these patients participated in the safety evaluation. In total, 98% of the patients participating in the evaluation had a neurological exam by a consultant neurologist and an MRI exam.

On February 28, 2005, Biogen Idec and Elan announced that they voluntarily suspended TYSABRI from the U.S. market and all ongoing clinical trials based on reports of PML, a rare and potentially fatal, demyelinating disease of the central nervous system.

**About Elan**

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**About Biogen Idec**

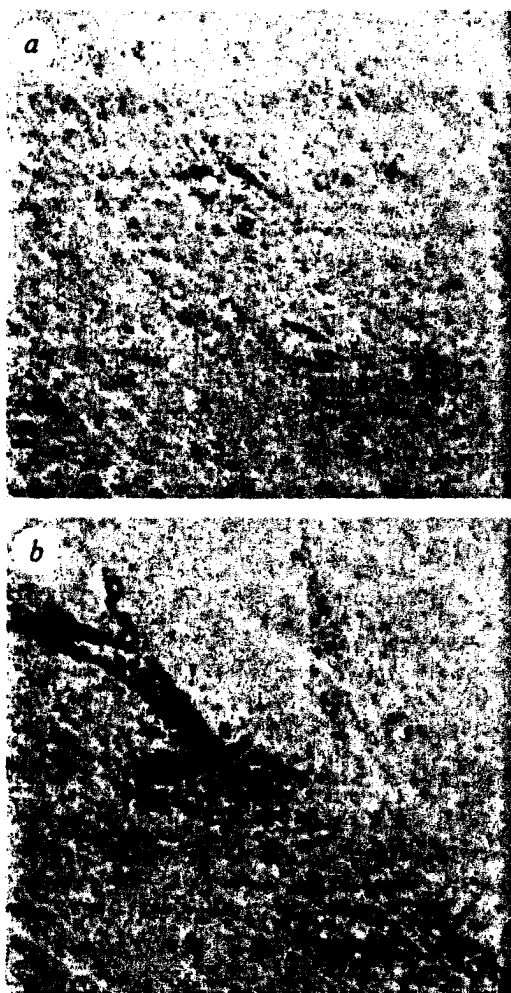
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## **EXHIBIT 10**

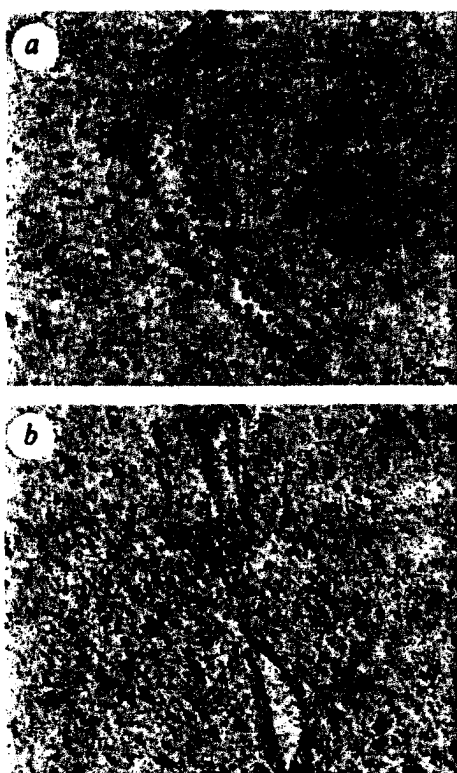






**FIG. 1** Lymphocytes and monocytes infiltrate venules in the brainstem of Lewis rats during EAE. Immunostained frozen sections of brainstem taken from Lewis rats exhibiting tail and hind limb paralysis caused by EAE ( $\times 70$  magnification). Sections were treated with: *a*, no primary antibody; *b*, monoclonal antibody OX-1, against CD45 which is expressed on all leukocytes; *c*, monoclonal antibody ED1, which recognizes circulating monocytes. Infiltrating leukocytes, comprised mostly of T cells ( $CD2^+$ , not shown) and circulating monocytes ( $ED1^+$ ), form 'cuffs' around numerous venules in the brainstem, spinal cord and a few vessels in the cortex.  $ED1^-$  and  $CD45^-$  positive cells were always found in brain sections from animals exhibiting paralysis, and were never seen in brain sections from control animals.

**METHODS.** EAE was induced in Lewis rats by injecting  $8 \times 10^6$  cells of a  $CD4^+$  T-cell clone specific for myelin basic protein (K-BP2). Production and maintenance of the T-cell clone was as previously described<sup>8</sup>. Animals exhibited tail or tail and hind limb paralysis on days 4 and 5, and brains were removed on day 6 for analysis. Immunohistochemistry was done on cryostat sections of brain tissue with Vectastain ABC (Vector Laboratories, Burlingame, California). The monoclonal antibodies, OX-1, OX-34 (against rat  $CD2$ ), and ED1 were obtained from Bioproducts for Science.



**FIG. 2** *In vitro* binding of human U937 monocytic cells to inflamed vessels in rat EAE brain. *a*, ( $\times 70$  magnification). Cryostat sections of EAE rat brain were exposed to U937 cells (ATCC number CRL 1593). Cells bound exclusively to inflamed venules and occasional arterioles. Attached cells are easily discernable because they stain more darkly than the sectioned tissue and because they are in a different focal plane. Several observations suggest that U937 bound to endothelium exposed in the profile of the inflamed vessel. (1) Binding was always to the lumen of the inflamed vessels; (2) under high power with differential focusing, U937 was consistently localized over endothelial cells; (3) U937 did not appear to interact with leukocytes surrounding the vessel, as there was no binding to the vessel where the lumen was out of the plane of section, nor to leukocytes that had migrated into the brain, away from the vessel. U937 also bound to the lumen of small arterioles in the EAE brain, which were never cuffed by endogenous leukocytes. *b*, In the same experiment, U937 cells were pretreated with anti- $\alpha 4$  integrin (HP2/1) and exposed to an adjacent section of EAE brain ( $\times 70$  magnification). HP2/1 inhibited U937 binding to the inflamed venules by greater than 95% (Table 1).

**METHODS.** Adhesion was assayed using freshly cut, unfixed,  $10 \mu m$  sections of EAE or normal rat brain. Leukocytes, suspended in RPMI 1640 medium (with 10 mM HEPES and 5% FBS) at a final concentration of  $10^7$  cells  $ml^{-1}$ , were layered over each section, the slides were immediately placed on a metal tray supported by ice and gyrated at 60 r.p.m. for 30 min. Some assays were at  $25^\circ C$ . Details of the assay have been previously described<sup>30</sup>. Human lymphocytes were isolated from EDTA-treated blood with Lymphoprep (Nycomed AS, Oslo), monocytes with Nycodenz (Nycomed AS), and neutrophils with Mono-Poly Resolving Medium (Flow Laboratories, Irvine, Scotland). Mouse and rat lymphocytes were isolated by crushing mesenteric and cervical lymph nodes and flushing with RPMI/HEPES/serum containing  $40 \mu g \text{ ml}^{-1}$  DNase.

was obtained with human peripheral blood monocytes and lymphocytes, and with freshly isolated rat and mouse lymphocytes. Human peripheral blood neutrophils did not bind to EAE vessels.

Monoclonal antibodies against leukocyte adhesion receptors were examined for inhibitory activity in the *in vitro* section assay (Table 1). The attachment of U937 cells was almost completely inhibited by an antibody against human  $\beta 1$  integrin. The  $\beta 1$  integrins are a family of heterodimeric adhesion receptors, also known as VLA antigens<sup>9,10</sup>. These molecules share a common  $\beta$  chain ( $\beta 1$ ) in conjunction with six unique  $\alpha$  chains. U937 expresses  $\alpha 3$ ,  $\alpha 4$ ,  $\alpha 5$  and  $\alpha 6$  of the  $\beta 1$  integrins (Table 1). Function-blocking,  $\alpha$  chain-specific antibodies against these molecules were tested for inhibition of U937 binding to EAE vessels; anti- $\alpha 4$  (clone HP2/1) produced greater than 95% inhibition (Fig. 2 and Table 1a), whereas anti- $\alpha 3$ , anti- $\alpha 5$  and anti- $\alpha 6$  were without significant effect, even when administered in combination (Table 1a). Thus,  $\alpha 4\beta 1$  integrin is required for U937 adhesion to EAE vessels. These results were confirmed with freshly isolated rat and mouse lymphocytes and with lymphocytes and monocytes from human peripheral blood (Table 1b).

$\alpha 4\beta 1$  integrin has two distinguishable binding domains, one that mediates adhesion to fibronectin (FN) and another that binds the endothelial ligand VCAM-1 (refs 11, 12; INCAM-110, ref. 13). HP2/1, which prevented U937 binding to EAE vessels, inhibits both functional activities of  $\alpha 4$  integrin<sup>14</sup>. Surprisingly, two antibodies that selectively inhibit the FN-binding activity of  $\alpha 4$  integrin (P4G9 and HP1/7), enhanced U937 attachment to the EAE vessels. P4G9 also enhanced vessel binding when combined with anti- $\alpha 5$  integrin (Table 1a), whereas this combi-

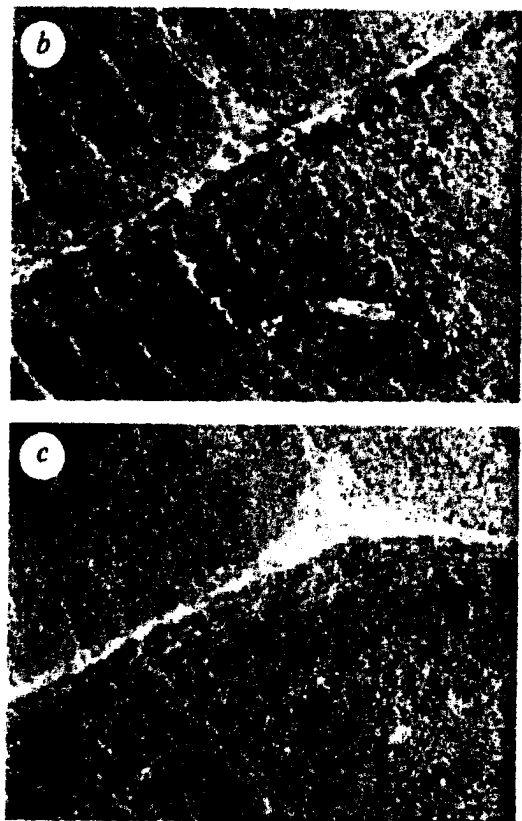
nation of antibodies inhibited U937 binding to FN by over 90% (not shown). These results suggest that the FN-binding activity of  $\alpha 4$  integrin is not directly involved in U937 adhesion to EAE vessels *in vitro*. Whether the known endothelial ligand for  $\alpha 4\beta 1$  integrin, VCAM-1, is expressed on the EAE vessels awaits production of appropriate reagents, but VCAM-1 has been detected on inflamed venules in mouse brain (B. Engelhardt and E. C. Butcher, personal communication) and at other sites of inflammation *in vivo*<sup>15,16</sup>.

Antibodies against many other leukocyte adhesion receptors were without effect on U937 or lymphocyte binding to EAE vessels (Table 1). Notable among these were anti-L-selectin (MEL-14), anti-CD 44 (Hermes-3), and 1B.2.6, which have been shown to inhibit lymphocyte attachment to venules in sections of lymph node (MEL-14, ref. 17) or Peyer's patches (CD-44, refs 18, 19, and 1B.2.6, ref. 20). Anti- $\beta 2$  integrin had little or no effect at either 4 °C or 25 °C (the activity of the  $\beta 2$  integrins has been reported to be temperature dependent), whereas HP2/1 produced almost complete inhibition at either temperature. These results suggest that  $\alpha 4\beta 1$  integrin has a prominent role in leukocyte adhesion to the inflamed brain venules. Other adhesion molecules are likely to work in conjunction with  $\alpha 4\beta 1$  integrin for effective leukocyte attachment and migration across the vessel wall *in vivo*. For example, the  $\beta 2$  integrins strengthen leukocyte adhesion after initial binding and have been implicated in subsequent leukocyte transmigration<sup>22</sup>. ICAM-1, a ligand for the  $\beta 2$  integrins<sup>23</sup>, has been observed on inflamed venules during EAE<sup>24-26</sup>.

As the anti- $\alpha 4$  integrin antibody, HP2/1, blocked lymphocyte and monocyte binding to EAE vessels *in vitro*, the effect of this antibody on the progression of EAE was tested *in vivo*

a Experiment 1				
Treatment	Number of animals with paralysis			
	Day 5	Day 6	Day 7	
No antibody	4/6	5/6	4/6	
HP2/1 (1.2 mg)	0/6	0/6	0/6	
MOPC (1.2 mg)	6/6	6/6	5/6	
Experiment 2				
Treatment	Number of animals with paralysis			
	Day 4	Day 5	Day 6	
No antibody	5/5	5/5	5/5	
HP2/1 (1.0 mg)	0/4	2/4	2/4	
OX-1 (1.0 mg)	5/5	5/5	5/5	
OX-7 (1.0 mg)	5/5	5/5	5/5	
Experiment 3				
Treatment	Number of animals with paralysis			
	Day 4	Day 5	Day 6	
No antibody	6/6	6/6	6/6	
HP2/1 (0.4 mg)	1/5	2/5	2/5	
HP2/1 (0.8 mg)	1/5	2/5	1/5	
HP2/1 (1.6 mg)	0/6	0/6	2/6	

FIG. 3 *In vivo* administration of anti- $\alpha 4$  integrin prevents accumulation of leukocytes in the CNS during EAE and prevents paralysis. a In each experiment, the T-cell clone was administered on day 0. On day 2, animals received an intraperitoneal injection of PBS, the indicated amount of purified anti- $\alpha 4$  integrin, or the indicated amount of purified control antibody. All antibodies were mouse IgG<sub>1</sub>. Disease was defined by complete tail or tail and hind limb paralysis. In animals that developed disease, paralysis began on day 4 or 5, peaked on day 5 or 6, and steadily diminished thereafter. Two additional experiments gave comparable results. Circulating levels and differential counts of white blood cells were indistinguishable between HP2/1-treated and PBS control animals when measured on days 3, 4 and 7 (day 3 is one day after antibody administration and one day before the earliest onset of paralysis). Bulk quantities of HP2/1 were purchased from AMAC; MOPC from Sigma; OX-1 and OX-7 from Bioproducts for Science. b, c. Brains were removed from several diseased EAE and healthy anti- $\alpha 4$  integrin-treated EAE rats from experiments 2 and 3 on day 6 ( $\times 70$  magnification). The micrographs show sections of comparable regions of the



brainstem and cerebellum, immunostained with anti-CD45 (OX-1) to illustrate the degree of leukocyte infiltration. There was extensive infiltration in brains from diseased EAE animals (b), whereas leukocytes could not be detected in the EAE rats treated with anti- $\alpha 4$  integrin (c).



(Fig. 3a). Two days after administering the inflammation-inducing T-cell clone, animals were given a single intraperitoneal injection of HP2/1 or of control antibodies. Anti- $\alpha 4$  integrin completely prevented the development of paralysis in 75% of the treated animals; in those that developed disease, paralysis was delayed and its severity was reduced (Fig. 3a). Isotype-matched control antibodies that bind to the surface of rat monocytes and T-cells at higher amounts than HP2/1 did not affect the onset or severity of disease (Fig. 3a). The protective effect of HP2/1 was dose dependent. Nearly all animals were protected by higher concentrations of antibody (Fig. 3a). Immunohistochemically, brainstems from EAE animals injected with control antibodies revealed extensive leukocyte infiltration (Fig. 3b), whereas infiltration was not detected in brains from EAE animals treated with anti- $\alpha 4$  integrin.

Several mechanisms might explain the strong protective effect of anti- $\alpha 4$  integrin against infiltration of the CNS by host leukocytes and the progression of EAE. First, results with the *in vitro* section assay indicate that anti- $\alpha 4$  integrin inhibits the adhesive interactions of lymphocytes and monocytes with inflamed brain vessels, and thus may prevent circulating leukocytes from entering the CNS. Second, although the data suggest that the FN-binding site of  $\alpha 4\beta 1$  integrin is not involved in leukocyte adhesion to inflamed vessels, FN interactions may be important for leukocyte migration across the vessel wall<sup>27</sup>. If so, blocking this interaction with the antibody HP2/1 could have contributed to the *in vivo* effects. Third,  $\alpha 4\beta 1$  integrin can augment antigen-specific activation of T cells<sup>28,29</sup>. As EAE was initiated by injection of an antigen-specific T-cell clone, it is possible that antibody treatment inhibited necessary signals delivered to the clone through  $\alpha 4\beta 1$ . This is unlikely because anti- $\alpha 4$  integrin was not administered until 2 days after injection of the T-cell clone, by which time the T cells would have already entered the CNS and initiated disease. Thus, we favour the hypothesis that antibody treatment blocked the entry of host lymphocytes and monocytes that would have normally infiltrated the brain in response to inflammation initiated by the T-cell clone. Experiments with control antibodies rule out the trivial explanation that any antibody reactive with circulating lymphocytes and monocytes would affect EAE (Fig. 3). Furthermore, absolute levels and relative counts of lymphocytes and monocytes were not affected by the antibody at any time during the course of disease (Fig. 3), indicating that the antibody did not induce leukocyte depletion.

Previous work on  $\alpha 4\beta 1$ -dependent cell adhesion has mainly involved studies with endothelium that has been grown and stimulated in culture. The *in vitro* section assay described here extends those observations by showing that  $\alpha 4\beta 1$  integrin is crucial for the adhesion of leukocytes to vessels that have been activated *in vivo*. Furthermore, *in vivo* administration of anti- $\alpha 4$  integrin prevented paralysis associated with the pathogenic inflammation of EAE. Therapy based on inhibiting  $\alpha 4\beta 1$  integrin, or the ligand for this receptor on brain endothelium, may prove effective in treating inflammatory diseases of the CNS. □

15. Briscoe, D. M. et al. *Transplantation* **51**, 537-539 (1991).
16. Koch, A. E. et al. *Lab. Invest.* **64**, 313-320 (1991).
17. Gallatin, W. M., Weissman, I. L. & Butcher, E. C. *Nature* **304**, 30-34 (1983).
18. Jalkanen, S., Bargatze, R. F., de los Toyos, J. & Butcher, E. C. *J. Cell Biol.* **105**, 983-990 (1987).
19. Picker, L. J., Nakache, M. & Butcher, E. C. *J. Cell Biol.* **109**, 927-937 (1989).
20. Chin, Y.-H., Cai, J.-P. & Johnson, K. *J. Immun.* **145**, 3669-3677 (1990).
21. Lawrence, M. B. & Springer, T. A. *Cell* **65**, 859-874 (1991).
22. Lusinskas, F. W. et al. *J. Immun.* **146**, 1617-1625 (1991).
23. Diamond, M. S., Staunton, D. E., Marlin, S. D. & Springer, T. A. *Cell* **65**, 961-972 (1991).
24. Rame, C. S., Cannella, B., Duijvestijn, A. M. & Cross, A. H. *Lab. Invest.* **63**, 476-490 (1990).
25. Wilcox, C. E. et al. *J. Neuroimmun.* **30**, 43-51 (1990).
26. Cannella, B., Cross, A. H. & Raine, C. S. *J. exp. Med.* **172**, 1521-1524 (1990).
27. Ferguson, T. A., Mizutani, H. & Kupper, T. S. *Proc. natn. Acad. Sci. U.S.A.* **88**, 8072-8076 (1991).
28. Damsle, N. K. & Aruffo, A. *Proc. natn. Acad. Sci. U.S.A.* **88**, 6403-6407 (1991).
29. Nojima, Y. et al. *J. exp. Med.* **172**, 1185-1192 (1990).
30. Yednock, T. A., Butcher, E. C., Stoolman, L. M. & Rosen, S. D. *J. Cell Biol.* **104**, 725-731 (1987).

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1. Paterson, P. Y. in *Textbook of Immunopathology* (eds Miescher, P. A. & Mueller-Eberhard, H. J.) 179-213 (Grune & Stratton, New York, 1976).
2. Alvord, E. C. Jr (ed.) *Experimental Allergic Encephalomyelitis: A Useful Model for Multiple Sclerosis* 1-511 (Liss, New York, 1984).
3. Wisniewski, H. M. & Keith, A. B. *Ann. Neurol.* **1**, 144-148 (1977).
4. Traugott, U., McFarlin, D. E. & Raine, C. S. *Cell Immun.* **99**, 395-410 (1986).
5. Zamvil, S. S. & Steinman, L. A. *Rev. Immun.* **8**, 579-621 (1990).
6. Ben-Nun, A., Wekerle, H. & Cohen, I. R. *Eur. J. Immun.* **11**, 195-199 (1981).
7. Hickey, W. F., Hsu, B. L. & Kimura, H. *J. Neurosci. Res.* **28**, 254-260 (1991).
8. Stamper, H. B. & Woodruff, J. J. *J. exp. Med.* **144**, 828-833 (1976).
9. Hynes, R. O. *Cell* **48**, 549-554 (1987).
10. Hemler, M. E. A. *Rev. Immun.* **8**, 365-400.
11. Ellices, M. J. et al. *Cell* **60**, 577-584 (1990).
12. Schwartz, B. R., Wayner, E. A., Carlos, T. M., Ochs, H. D. & Harlan, J. M. *J. clin. Invest.* **85**, 2019-2022 (1990).
13. Rice, G. E., Munro, J. M. & Bevilacqua, M. P. *J. exp. Med.* **171**, 1369-1374 (1990).
14. Pulido, R. et al. *J. Biol. Chem.* **266**, 10241-10245 (1991).

# **EXHIBIT 11**

## REVIEW

# Immune Therapy for Autoimmune Diseases

Lawrence Steinman

Our increasing understanding of the pathophysiology of autoimmune disease has revealed a number of checkpoints that can be targeted with immune therapy, including key mediators of lymphocyte adhesion and migration, destructive cytokines involved in tissue damage, and the complex of molecules critical in the presentation of self-antigen and the activation of autoaggressive T lymphocytes. In many organ-specific autoimmune diseases, the identity of the molecules attacked by T cells and autoantibodies is known and attempts are under way to tolerize the immune system with a high level of specificity to these targets.

The immune system, normally efficient in defeating external threats from the microbial world, at times directs its potent arsenal against the body's self-constituents, causing autoimmunity. Collectively, autoimmune diseases affect about 5% of North Americans and Europeans, two-thirds of whom are women (1). The diseases often involve distinct anatomic regions. For example, the immune system attacks the synovial lining of the joints in rheumatoid arthritis (RA), the thyroid gland in thyroiditis, the insulin-secreting beta cells of the pancreas in type 1 diabetes mellitus (T1DM), and the myelin sheath of the brain and the spinal cord in multiple sclerosis (MS). In systemic lupus erythematosus (SLE), there are protean manifestations with involvement of skin, kidneys, joints, and brain.

Although the causes of autoimmunity remain largely unknown, a prominent theory suggests a central role for infectious microbes in the etiology of these diseases. Thus, be-

cause certain microbes bear similar molecular structures to the molecules of self, a response to such a region on a microbe might also provoke autoimmunity—a concept termed molecular mimicry (1). Because the thymus is intimately involved in tolerance of T cells to self, some theories also invoke a failure in central thymic tolerance to explain autoimmunity (1). In some cases, the causes of autoimmunity are more apparent. For example, experimental therapy in one autoimmune setting can provoke yet another. Thus, treatment of MS patients with a monoclonal antibody to CD52, although showing some promise in ameliorating MS, has led to autoimmune hyperthyroidism in a third of the MS patients (2). Rarely, nonautoimmune diseases like cancer can also provoke autoimmunity. One example of this is in the paraneoplastic syndromes, in which an immune response to breast or ovarian cancer triggers an autoimmune reaction in other organs, including brain, retina, peripheral nerve, and muscle (3). In other instances, our natural physiology can prove the cause of an autoimmune response, such as in myasthenia, which may be transmitted to the fetus or

newborn through the passage of autoantibodies across the placenta (1). On the other hand, physiological changes such as pregnancy can suppress such autoimmune conditions as MS and RA (4, 5).

Despite detailed knowledge of the targets of attack and the cells perpetrating the autoimmune damage (Table 1), immunologists have so far had limited success in developing highly specific countermeasures to suppress pathologic responses without globally interfering with the immunity in the body. Nevertheless, some treatments have had considerable success. For example, blocking antibodies and soluble receptors specific for the inflammatory cytokine tumor necrosis factor (TNF) have had notable therapeutic efficacy in the treatment of RA (6). Similarly, antibodies that interfere with homing of white blood cells to the site of autoimmune inflammation in the brain have been used in treating sufferers of MS (7). Examples of more nonspecific therapy of autoimmunity now encompass recombinant cytokine molecules, such as  $\beta$ -interferon ( $\beta$ -IFN), for treatment of MS (8). In addition, familiar medications already widely used to treat other conditions, such as hypercholesterolemia (8), hypertriglyceridemia (9), allergy (10), and hypertension (11), also inhibit some of the main pathways in autoimmune inflammation. Such drugs have already shown promise in preclinical models of autoimmunity, as well as in early-stage clinical trials. This review explores the considerable progress in treating autoimmunity with cytokines or their antag-

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onists and with antibodies to homing molecules and discusses new approaches aimed at inducing antigen-specific tolerance in the context of autoimmune diseases (Fig. 1).

### Immune Therapies Targeting Cytokines and Their Receptors

Early research with synovial cultures from RA patients revealed that TNF was a critical mediator in the inflammatory response (6), and immunohistochemical studies of inflamed synovium from RA patients revealed TNF and TNF receptor at the site of disease. Furthermore, preclinical studies provided direct evidence that antibody to TNF could ameliorate arthritis, at least in mouse models (6). More important, however, administration of chimerized anti-TNF, or a soluble recombinant TNF receptor-immunoglobulin G (IgG) fusion protein, led to remarkable improvement of function in RA patients (12, 13) and has also proved beneficial in inflammatory bowel disease (14). Blockade of other inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and IL-15, has also proven a successful strategy in ameliorating RA, although the current experience with such drugs appears far less extensive than that seen with TNF blocking agents (15, 16).

Notwithstanding the success of TNF treatments, the use of anti-TNF drugs has revealed some problems. For example, it is not understood why about 50% of patients with longstanding RA do not respond to TNF inhibitors (6) and why blockade of proinflammatory cytokines can place some individuals at increased risk of infections such as tuberculosis (6). Strangely, while TNF blockade has been successful in improving function and clinical status in RA and Crohn's disease, the same medicines worsen MS (6, 17). This is most likely explained by the fact that, although excessive TNF is injurious for myelin-producing cells in the brain and spinal cord, it is also an important growth factor for these same cells (18). Many inflammatory cytokines are thus akin to the two-headed god, Janus: On the one hand they are mediators of damage, yet they have beneficial roles in repair as well (17).

Other approaches that target certain T cell populations with monoclonal antibodies to CD4 and to T cell receptors have been less impressive in RA and in MS (7). New enthusiasm is being generated for depleting B lymphocytes with antibodies to CD20, an approach that has been successful for treating lymphoma. Initial trials in RA are promising, and trials are being initiated in MS and SLE (19). Another hopeful approach for treatment of RA lies in the inhibition of the molecules present at the immune synapse between T cells and antigen-presenting cells, which are involved in antigen-specific activation of T cells. The synapse includes stimulatory molecules such as CD28, which interacts with CD80 and CD86 on the presenting

cell. Blockade of this interaction with a fusion protein-cytotoxic T-lymphocyte-associated antigen 4-IgG1 (CTLA4Ig), which also binds CD80 and CD86 with a high affinity, can prevent T cell activation and has been shown to improve the symptoms of RA in early clinical trials (20).

### Cytokines for Treatment of Autoimmunity

Interferon (IFN) has been used in treating MS, with the rationale that because these cytokines have antiviral activity, and because MS might be triggered by some as yet unknown virus, they could exert a therapeutic influence by this means. However, because administration of IFN $\gamma$  to MS patients has been found to exacerbate disease, the trial using this cytokine was halted. Subsequently, testing of  $\beta$ -IFN proved more successful, reducing the relapse rate of MS by 30% and slowing disease progression to a modest degree, with a measurable reduction in the number and volume of injured areas in the brain, as assessed by magnetic resonance scans (21, 22). Although  $\beta$ -IFN has both antiviral activity and a therapeutic effect in MS, direct proof that a particular viral pathogen

crobes at almost any location in our bodies. Once activated, lymphocytes migrating through blood vessels arrest their movement and bind to Velcro-like receptors along the vessel walls to initiate the process of penetrating the target organ (1, 26). It was hypothesized that lymphocytes express specific adhesion molecules that recognize other proteins that represent particular anatomic "addresses." Thus, because the key homing molecules—integrins and selectins—display a high degree of diversity, the particular integrin or selectin expressed is critical for entry to a particular anatomic site. As a consequence, it is conceivable that blocking a particular ligand/receptor interaction would be sufficient to abolish pathologic homing, yet leave lymphocytes free to move elsewhere. This has indeed turned out to be a very promising avenue, at least in preclinical models of autoimmunity (27). For example,  $\alpha$ 4-integrin on T lymphocytes allows these cells to recognize vascular cellular-adhesion molecule 1 (VCAM-1), facilitating migration to the central nervous system (27). Although VCAM-1 is usually not expressed at high levels on blood vessels in the brain, in animal models and in

Table 1. Specific targets of the immune response in organ-specific autoimmune disease.

Disease	Immune target
Myasthenia gravis	Acetylcholine receptor
Multiple sclerosis	MBP, MOG, PLP
Pemphigus vulgaris	Desmoglein-3
Rheumatoid arthritis	Filaggrin
Hashimoto's thyroiditis	Thyroid peroxidase, thyroglobulin
Graves' disease	Thyrotropin receptor
Type 1 diabetes	Glutamic acid decarboxylase, insulin, HSP 60

triggers MS itself has not so far been forthcoming (8, 17, 21, 22). Thus, other mechanisms of action for  $\beta$ -IFN's success in this disease might be considered, including reduction of metalloprotease activity, which is required for lymphocyte migration to the brain (23), or reduction of major histocompatibility complex (MHC) class II expression in the brain, a prerequisite for triggering myelin-reactive T cells (24).

Systemic administration of recombinant cytokines has also been tried with some success in other autoimmune conditions. For example, in early clinical trials with the autoimmune skin disease psoriasis, clinical improvement and amelioration of skin lesions was observed with administration of IL-4 (25). Within the lesions, the number of (presumably pathogenic) IFN $\gamma$ -producing T cells was markedly reduced, and the levels of two cytokines involved in psoriasis, IL-8 and IL-19, were also reduced in the lesions.

### Promising Results of Clinical Trials with Antibodies Against Homing Receptors

Cells of the immune system represent highly mobile elements, primed to defend against mi-

human MS its expression is increased (27). Indeed, administration of  $\alpha$ 4-integrin in experimental autoimmune encephalomyelitis (EAE) was able to ameliorate disease and block encephalitogenic T cell clones from entering the brain (27). In the sequence of events,  $\alpha$ 4-integrin interacts first with VCAM-1 on the surface of the blood vessel and then with the secreted cytokine osteopontin, which is expressed in the extracellular matrix (28). This interaction is critical in the migration of lymphocytes into the brain itself and suggests that osteopontin may also play a critical role in MS and in autoimmune demyelination (29, 30, 31).

The  $\alpha$ 4-integrin is also critical for homing to a range of organs in other models of autoimmune disease, including spontaneous T1DM in nonobese diabetic mice, as well as in models of RA, ulcerative colitis, and asthma (32). Thus far, however, the strategy for treatment of autoimmune disease by blockade of homing molecules has not shown the level of exquisite specificity originally envisioned. To achieve this, further refinements, such as the development of drugs able to react with specific regions

on  $\alpha 4\beta 1$ -integrin rather than, for example,  $\alpha 4\beta 7$ -integrin, may allow for improved specificity in blocking homing to the brain rather than to the intestine.

At the same time, antibody to  $\alpha 4$ -integrin has shown some degree of success in phase 2 clinical trials of MS and in inflammatory bowel disease (7, 32). Because the same antibody blocks the ability of lymphocytes bearing  $\alpha 4\beta 1$ -integrin to bind to VCAM-1 and enter the central nervous system, as well as the ability of  $\alpha 4\beta 7$ -integrin to bind to the intestinal mucosal addressin cell adhesion molecule 1 (MadCAM-1), the treatment can influence pathology in both organs. In inflammatory bowel disease, the remission rate was twice as high in individuals receiving the antibody as in those receiving placebo (33), and in MS, the antibody decreased the fre-

quency of clinical relapses by 50%, also reducing the frequency of injured areas on magnetic resonance scans (7).

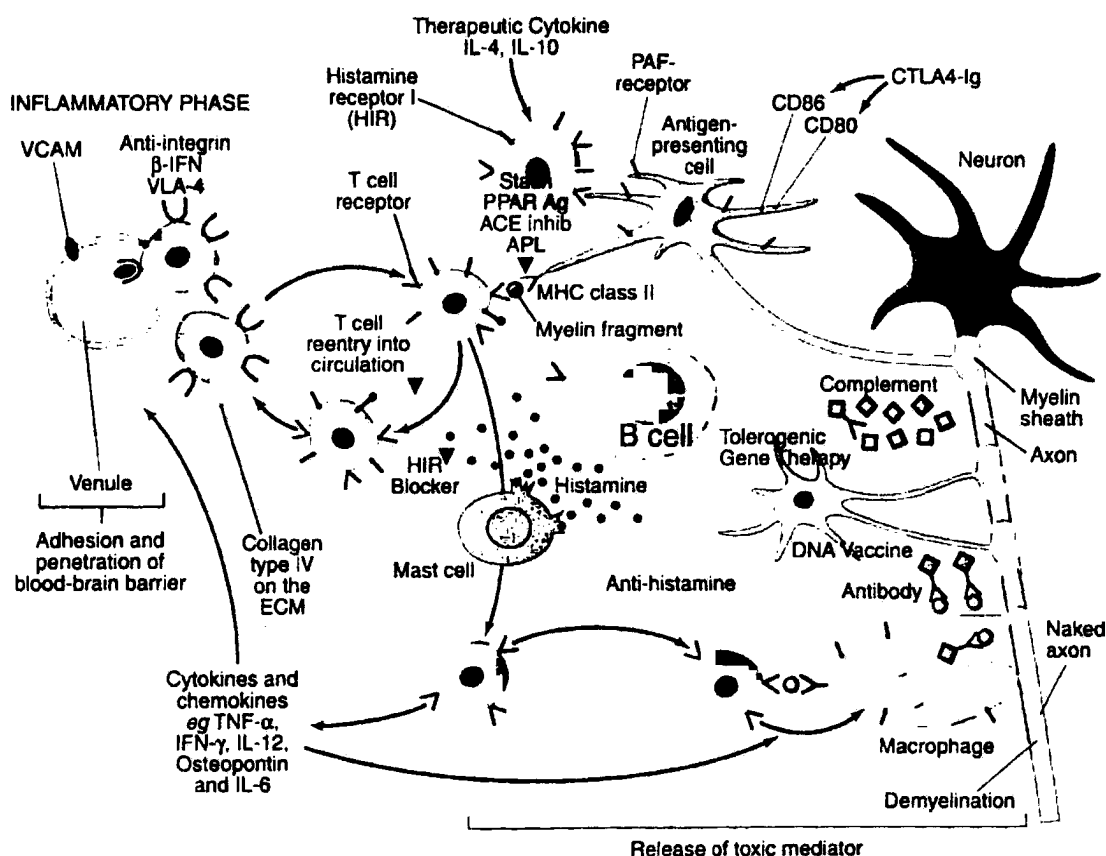
At this point, there are two main concerns with the above approach. As discussed, the importance of the  $\alpha 4$ -integrin in homing to more than one anatomic site means that there is at least a theoretical concern that recipients of the therapy would become generally compromised in their ability to fight infection. This concern has been borne out in a phase 2 trial in MS, in which an increased rate of pharyngitis, a form of upper respiratory tract infection, was observed (7). A second concern is that upon cessation of blockade of integrins, cells might again home to the site of disease. This is something that has been observed in some MS patients after discontinuation of the drug (7).

### Commonly Used Drugs Can Provide Cost-Effective Potential Therapies for Autoimmunity

Statins lower cholesterol by virtue of their ability to inhibit one of the critical enzymes, HMG-CoA reductase, and are taken by millions of individuals worldwide. Remarkably, in animal models of autoimmunity such as EAE and collagen-induced arthritis, these drugs have also proven protective (8, 34). Along with their other effects, statins reduce the inducible expression of MHC class II molecules and block the expression of costimulatory molecules necessary for the induction of autoaggressive T cells (34). They can also shift the balance of cytokines produced by autoaggressive T cells from T helper-1 ( $T_H1$ ) proinflammatory cytokines, such as IFN- $\gamma$  and TNF, to  $T_H2$ -type cytokines, including IL-4, IL-5, IL-10, and IL-13 (31). Encouragingly, in pilot trials using statins

to treat MS, inflammatory lesions were measurably reduced (35), and large-scale controlled trials of statins are now under way for both MS and RA.

Similarly, other drugs, such as peroxisome proliferation-activated receptor  $\alpha$  (PPAR- $\alpha$ ) agonists (widely prescribed to treat hypertriglyceridemia) and blockers of angiotensin used in treating hypertension, have demonstrable anti-inflammatory properties. Furthermore, these drugs have been shown to inhibit clinical disease and pathology in models of autoimmunity such as EAE (9, 11). As with statins, PPAR- $\alpha$  agonists are capable of shifting the cytokine profile from  $T_H1$  to  $T_H2$ , and early experiments with angiotensin blockers have indicated that they have similar properties (9). Histamine-1 receptors are found on  $T_H1$  T cells, and administration of histamine antagonists can block the development of EAE, again with an altered cytokine balance from  $T_H1$  to  $T_H2$  (10).



**Fig. 1.** The pathogenesis of multiple sclerosis. There are many similarities between the pathogenesis of MS and of other organ-specific autoimmune diseases such as T1DM, inflammatory bowel disease, and RA. Each step in the process is associated with a potential strategic checkpoint where therapy could be targeted. An antibody to  $\alpha 4$ -integrin blocks lymphocytes from homing to the blood vessel wall, where they bind to VCAM-1 in MS and RA, or to MadCAM-1 in inflammatory bowel disease. In MS,  $\beta$ -interferon inhibits metalloproteases, impeding diapedesis through the extracellular matrix. Extracellular matrix proteins include osteopontin, which is blocked by antibody to  $\alpha 4$ -integrin. Inside the brain, inducible MHC class II is inhibited by statins. Proinflammatory cytokine production is blocked by histamine-1 receptor blockers, statins, PPAR- $\alpha$  agonists, and ACE inhibitors. MS and RA differ in that blockade of TNF is beneficial for RA but worsens MS. In MS, TNF has Janus-like qualities: It is proinflammatory and necessary for the replenishment of myelin. Other strategies aim at delivering suppressive cytokines like IL-4 or IL-10 directly to the immune system or to affected tissues. These strategies induce regulatory T cells,  $T_{reg}$  cells, that are capable of inhibiting autoaggressive T cells. Blockade of costimulation with CTLA4Ig has been effective at blocking activated autoreactive T cells. DNA vaccines and altered peptides tolerize T cells and reduce the spread of autoantibodies. Specific targeting of dendritic cells with antigen or autoaggressive T cells with genes encoding IL-4 and IL-10 has been attempted with some success in animal models.



The importance of these results lies in the fact that antihistamines are widely used for the treatment of allergy and are taken by millions of individuals.

Such results are encouraging, because they suggest that many commonly used medications for a variety of conditions might be effectively combined with new regimes to treat autoimmune disease. Finally, it is interesting to speculate that since atherosclerosis may have an autoimmune component in its pathogenesis (1), the role of angiotensin blockers, statins, and PPAR agonists may be to protect from myocardial infarction and stroke, not only by lowering blood pressure, lipids, and cholesterol but also by blocking the potential autoimmune components of atherogenesis (36).

### Antigen-Specific Therapy for Autoimmunity

The identity of the target antigens in several major autoimmune diseases has been characterized, including T1DM, pemphigus vulgaris (PV), myasthenia gravis (MG), and MS. Thus, in T1DM, the immune system targets four major antigens, insulin, IA-2, glutamic acid decarboxylase (GAD), and heat shock protein 60 (hsp-60). As a consequence, the insulin-producing islets of Langerhans of the pancreas are destroyed. If a child at risk for T1DM, by virtue of having a first-degree relative with the disease, develops antibodies to insulin, GAD, and IA-2, then the probability of that child developing T1DM in the next five years approaches 100% (37). In PV, the immune system attacks desmoglein-3, a protein that allows epithelial cells to adhere to each other in the skin. Antibodies to desmoglein-3 cause widespread blistering by interrupting these intercellular "welds," and if autoantibodies from individuals with PV are transferred to mice, the mice will also develop skin blisters (38). In MG, antibodies are produced against the acetylcholine receptor at the neuromuscular junction (1, 17, 39); in the case of MS, antibodies and T cells are detected that react to various myelin proteins and lipids (1, 8, 17).

Despite such detailed knowledge of the target antigens in many autoimmune diseases (Table 1), immunologists and clinicians have had a difficult time silencing the destructive immune responses directed to self-antigens. A prime reason has been that the immune response "broadens" during the course of disease. Thus, an immune response to a single epitope on an organ-specific antigen at the start of disease can trigger immune responses to neighboring epitopes on the same molecule or to other epitopes on nearby molecules. This process, termed epitope spreading, ultimately draws in a larger repertoire of immune responses toward other autoantigens, ultimately enhancing the level of tissue destruction.

One strategy to combat the increase in breadth of immune response during the pro-

gression of an autoimmune disease would be to devise therapies that would simultaneously tolerize against multiple immune responses. One such solution to the problem of epitope spreading came with an invention made more than 30 years ago. In the 1970s, a random copolymer of the amino acids glutamate, tyrosine, alanine, and lysine, now termed glatiramer acetate, was initially designed to mimic the composition of myelin basic protein (MBP). It was effective in ameliorating EAE and was taken into clinical trials of MS, where it reduced the relapse rate by 30% (40). Fortunately, the random nature of the copolymer tolerized against a variety of different myelin antigens (40, 41). Glatiramer was perhaps the first example of an altered self-antigen, now termed an altered peptide ligand (APL). For example, one of the combinations in glatiramer, EYYK, is capable of tolerizing mice to MBP and preventing paralysis in the EAE model of MS (42). Another mechanism, not envisioned at the time glatiramer acetate was invented, is its capacity to induce a  $T_H2$ -dominated response to myelin antigens (43).  $T_H2$  responses are associated with allergic-type reactions, and indeed about 10% of individuals taking glatiramer acetate develop allergic reactions, including bronchial constriction and local skin rashes (44). The development of clinical manifestations of allergy, when shifting immunity from  $T_H1$  to  $T_H2$ , is a vivid demonstration of the application of the  $T_H1/T_H2$  "paradigm" in humans (45).

More recently, an APL of MBPp83-99 was constructed by revising the main contact sites that this epitope has with the T cell receptor. APLs can induce a  $T_H1$  to  $T_H2$  shift in cytokine production in animal models of autoimmunity. This is a potentially important protective feature of APL, because  $T_H2$  cytokines have been shown to suppress immune responses to neighboring antigens that arise by epitope spreading. For example, by inducing IL-4, an APL for MBP can reverse ongoing EAE, induced by a different myelin molecule (46). In a phase 2 placebo-controlled clinical trial, an APL was able to shift the response of MBP-specific T cells, favoring  $T_H2$  cytokines over  $T_H1$  cytokine production (44). At lower doses, reduction in brain lesions was seen, while at higher doses, exacerbations of disease were noted in three patients (47). Allergic phenomena including skin rashes were seen following induction of a  $T_H1$  to  $T_H2$  shift in 10% of the patients (44). Avoiding such allergic phenomena will be a challenge in the development of this therapeutic strategy for shifting the balance of dominant cytokines from  $T_H1$  to  $T_H2$ .

Three other trials of antigen-specific therapy for T1DM are under way or have been completed recently. These include phase 2 trials with GAD and with an APL of insulin (48) and of hsp-60 (49). In the trial with the APL for

hsp-60, decreased exogenous insulin use was observed in diabetics, as well as a shift toward  $T_H2$  immunity (49). In a trial of insulin administered either orally or parenterally, no benefit was seen in preventing the development of T1DM in first-degree relatives of patients who had already developed diabetes (50).

Antigen-specific therapy of autoimmune disease has been attempted with oral administration of myelin antigens in MS, collagen in RA, and insulin in T1DM. Despite success in the prevention of disease in animal models of autoimmunity, in which antigen was fed to the animals at the time of disease induction, clinical trials attempting to treat ongoing disease in humans have thus far been unsuccessful (51). It is well established, however, that the oral route is highly effective in animals for desensitization of immune responses (52, 53). Antigen-specific T cells can be activated within 6 hours of feeding the antigen, and repeated administration of low doses of antigen by the oral route can diminish the number of effector T cells in the circulation that are capable of responding to that antigen (52). Finally, regulatory T cells ( $T_{reg}$ ) secreting transforming growth factor beta, IL-10, and other suppressive  $T_H2$  cytokines have been shown to be induced by oral feeding of self-antigen (53).

Such experiments point to the continued promise of using oral delivery to induce tolerance. Thus, despite the lack of success, so far, in using the oral route for tolerance induction in humans, powerful regulatory mechanisms clearly exist at mucosal sites, and it is conceivable that these may prove important to exploit for future immune-based therapy.

Another promising method to induce tolerance to islet cell antigens in T1DM involves the administration of antibodies to CD3. By engaging CD3 in the immune synapse on T cells (17), these antibodies are able to deviate the immune response to islet antigens toward  $T_H2$  cytokine production and to activate regulatory T cells capable of restraining the autoreactive responses (54). In a small trial with antibodies to CD3 in patients with T1DM treated within 6 weeks of diagnosis, an improved metabolic control of glucose was observed over the first year of disease (55). Various strategies, including administration of APL, blocking CTLA4, and use of anti-CD3, have proven efficient at inducing regulatory  $T_{reg}$  cells. The effectiveness of  $T_{reg}$  at restraining autoaggressive T cells in experimental settings (20, 43, 54, 56) suggests that it may some day be possible to harness the regulatory capacity of these cells in the treatment of a range of autoimmune diseases.

Recent studies with large-scale microarrays, designed to analyze the spread of the antibody response in EAE, have demonstrated that as demyelinating disease progresses, antibodies develop toward multiple myelin

proteins (57). This again emphasizes the challenge posed by epitope spreading when investigators try to devise therapeutic countermeasures. One method of tolerizing to multiple myelin components on a large scale has been developed with DNA plasmids encoding several myelin antigens (57). When these DNA plasmids were administered to mice after the first attack of EAE, they reduced the subsequent relapse rate by greater than 50%. At the same time, a reduction was seen in the spreading of antibodies toward multiple myelin antigens, including MBP, proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG) (57). A phase I trial with DNA vaccines designed to tolerize against myelin proteins has been approved by the Food and Drug Administration.

Dendritic cells (DC) are already being targeted as a means of boosting immunity to infectious pathogens and cancer antigens, and competing strategies aimed at delivering suppressive cytokines to DC or to T cells are also being used with some success in treating animal models of autoimmunity (58). For example, by using specific receptors expressed by DC, it has been possible to target small amounts of antigen to these specific subsets of the cells without incurring their activation, thus attaining tolerance rather than immunity (59). Such experimental studies suggest that DC may be successfully used in guiding tolerizing therapies for autoimmune disease in the clinic.

#### Future Directions

A number of partially effective treatments for major autoimmune diseases have now been developed, and most of the approved treatments have, thus far, brought considerable relief to as many as two-thirds of patients with autoimmune diseases such as RA and MS. Nevertheless, none of the approved

treatments yet have the exquisite specificity to neutralize the highly restricted set of immune responses that characterize most autoimmune conditions. Furthermore, they carry substantial economic cost, with an annual price tag of about \$5 billion in the United States. Although there is clearly a net benefit in alleviating suffering and disease progression, if such "high-tech" drugs turn out to be curative only in synergistic combinations, we may see an even more substantial rise in the fiscal costs of therapy. We should keep in mind that many drugs are generic and already approved for non-autoimmune diseases and that these may prove efficacious when used alone or in combination with the newer drugs designed to treat autoimmunity. Finally, some day a true "cure" for the ailments of autoimmunity may be developed—perhaps based on antigen-specific immune therapy—that might eventually prove as cost effective as vaccination for infectious diseases.

#### References and Notes

1. L. Steinman, *Sci. Am.* 269, 106 (1993).
2. A. Coles et al., *Lancet* 354, 1691 (1999).
3. R. Darnell, J. Posner, *N. Engl. J. Med.* 348, 1543 (2003).
4. C. Confavreux et al., *N. Engl. J. Med.* 339, 285 (1998).
5. M. Ostensen, P. Villiger, *Transpl. Immunol.* 9, 155 (2002).
6. M. Feldmann, R. Maird, *Nature Med.* 9, 1245 (2003).
7. D. Miller et al., *N. Engl. J. Med.* 348, 15 (2003).
8. S. Zamvil, L. Steinman, *Neuron* 38, 685 (2003).
9. A. Lovett-Racke et al., *J. Immunol.* 172, 5790 (2004).
10. R. Pedotti, J. DeVoss, L. Steinman, S. Galli, *Trends Immunol.* 24, 479 (2003).
11. C. Constantinescu, E. Ventura, B. Hilliard, A. Rostami, *Immunopharmacol. Immunotoxicol.* 17, 471 (1995).
12. M. Elliott et al., *Lancet* 344, 1105 (1994).
13. L. Moreland et al., *N. Engl. J. Med.* 337, 141 (1997).
14. H. van Dulleman et al., *Gastroenterology* 109, 129 (1995).
15. W. Arend, J. Dayer, *Arthritis Rheum.* 38, 151 (1995).
16. N. Nishimoto et al., *J. Rheumatol.* 30, 1426 (2003).
17. L. Steinman, *Nature Immunol.* 5, 575 (2004).
18. H. Arnett et al., *Nature Neurosci.* 4, 1116 (2001).
19. S. De Vita et al., *Arthritis Rheum.* 46, 2029 (2002).
20. J. Kremer et al., *N. Engl. J. Med.* 349, 1907 (2003).
21. D. Paty, *Ann. Neurol.* 36, 5113 (1994).
22. G. Comi et al., *Lancet* 357, 1576 (2001).
23. O. Stuve et al., *Ann. Neurol.* 40, 853 (1996).
24. C. Devaliyoth et al., *J. Biol. Chem.* 268, 18794 (1993).
25. K. Ghoreschi et al., *Nature Med.* 9, 40 (2003).
26. E. Butcher, L. Picker, *Science* 272, 60 (1996).
27. T. Yednock et al., *Nature* 356, 63 (1992).
28. D. Denhardt et al., *J. Clin. Invest.* 107, 1055 (2001).
29. D. Chabas et al., *Science* 294, 1731 (2001).
30. T. Blom, A. Franzen, D. Heinegard, R. Holmdahl, *Science* 299, 1845a (2003).
31. L. Steinman et al., *Science* 299, 1845b (2003).
32. U. von Adrian, B. Engelhardt, *N. Engl. J. Med.* 348, 68 (2003).
33. S. Ghosh et al., *N. Engl. J. Med.* 348, 24 (2003).
34. S. Yousef et al., *Nature* 420, 78 (2002).
35. T. Vollmer et al., *Lancet* 363, 1607 (2004).
36. O. Ruiz-Ortega et al., *Hypertension* 38, 1382 (2001).
37. C. Verge et al., *Diabetes* 45, 926 (1996).
38. M. Un et al., *J. Clin. Invest.* 99, 31 (1997).
39. L. Steinman, R. Mantegazza, *FASEB J.* 4, 2726 (1990).
40. M. Sela, *Int. Rev. Immunol.* 18, 201 (1999).
41. R. Aharoni, D. Teitelbaum, R. Arnon, M. Sela, *Proc. Natl. Acad. Sci. U.S.A.* 96, 634 (1999).
42. P. Ruiz et al., *J. Immunol.* 167, 2688 (2001).
43. P. Duda et al., *J. Clin. Invest.* 105, 967 (2000).
44. L. Kappos et al., *Nature Med.* 6, 1176 (2000).
45. T. Mosmann, R. Coffman, *Annu. Rev. Immunol.* 7, 145 (1989).
46. L. Steinman, *J. Exp. Med.* 189, 1021 (1999).
47. B. Bielekova et al., *Nature Med.* 6, 1167 (2000).
48. D. Alleva et al., *J. Clin. Invest.* 107, 173 (2001).
49. I. Raz et al., *Lancet* 358, 1749 (2001).
50. P. Pozzilli, *Diabetes Metab. Res. Rev.* 18, 257 (2002).
51. H. Weiner, *Immunol. Today* 18, 335 (1997).
52. I. Gutgennan et al., *Immunity* 8, 667 (1998).
53. Y. Chen et al., *Science* 265, 1237 (1994).
54. J. Bach, L. Chatenoud, *Annu. Rev. Immunol.* 19, 131 (2001).
55. K. Herold et al., *N. Engl. J. Med.* 346, 1692 (2002).
56. C. Assmann, M. von Herrath, *Autoimmun. Rev.* 1, 190 (2002).
57. W. Robinson et al., *Nature Biotechnol.* 21, 1033 (2003).
58. A. Slavin et al., *Autoimmun. Rev.* 1, 213 (2002).
59. L. Bonifaz et al., *J. Exp. Med.* 196, 1627 (2002).
60. The support of the National Institutes of Health, the Phil N. Allen Trust, and the National Multiple Sclerosis Society is greatly appreciated. L.S. was cofounder of Neurocrine Biosciences—a publicly traded biotechnology company focusing on the interaction of the nervous system, the endocrine system, and the immune system—where he currently serves as a consultant and a member of its board of directors. L.S. is also a cofounder of Bayhill Therapeutics in Palo Alto, CA—a privately held company focusing on the use of DNA vaccines to tolerize the immune system.

## **EXHIBIT 12**

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**125104**

**MEDICAL REVIEW**

## CLINICAL REVIEW

Application Type BLA  
Submission Number 125104/0  
Submission Code Not applicable

Letter Date November 23, 2004  
Stamp Date May 24, 2004  
PDUFA Goal Date November 23, 2004

Reviewer Name Wilson W. Bryan, M.D.  
Acting Team Leader Name Ellis F. Unger, M.D.  
Division Director Name Marc K. Walton, M.D., Ph.D.  
Office Director Name Karen D. Weiss, M.D.  
Review Completion Date November 23, 2004

Established Name Natalizumab  
Proposed Trade Name Tysabri  
Therapeutic Class monoclonal antibody  
Applicant Biogen Idec, Inc.

Priority Designation P

Formulation recombinant humanized IgG4 antibody to  $\alpha$ 4-integrin  
Dosing Regimen 300 mg intravenous infusion every 4 weeks  
Indication treatment of relapsing forms of multiple sclerosis  
Intended Population relapsing multiple sclerosis

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

This licensing application is for accelerated approval of natalizumab, (proposed trade name: Tysabri), for the treatment of patients with relapsing forms of multiple sclerosis (MS), to reduce the frequency of clinical exacerbations. Two multicenter, randomized, double-blind, placebo-controlled studies (Studies 1801 and 1802) provide the primary evidence of safety and efficacy. Both studies are two years in duration; however, this regulatory action is based on results achieved through approximately one year in the ongoing studies.

Study 1801 enrolled subjects with active relapsing-remitting MS (RRMS). Most of these patients had never received any of the currently approved MS therapies. Study 1802 enrolled subjects with clinically active RRMS, who had been receiving a standard MS therapy (Interferon  $\beta$ -1a) on a weekly basis during the year prior to study entry. In both investigations, subjects had experienced at least one clinical relapse during the year prior to study entry, providing evidence of clinically active disease.

Subpart E of the BLA regulations (21 CFR 601 subpart E) allows accelerated approval of new biologics that provide meaningful therapeutic benefit over existing treatment for serious or life-threatening illnesses, based on a surrogate endpoint that is reasonably likely to predict clinical benefit. This application provides evidence of efficacy for only one year of natalizumab administration, based on reduction in MS relapse rates. For MS therapies, a relapse endpoint may be accepted as evidence of effectiveness; however, the clinical meaningfulness of a decrease in the relapse rate through only one year is uncertain. Drugs currently approved for MS have each demonstrated evidence of a benefit at 2 years in order to gain marketing approval. However, the magnitude of natalizumab's treatment effect at one year is quite robust, and is deemed reasonably likely to predict a clinical benefit at two years. Therefore, the effect at one year can be considered as a surrogate for an effect at two years. The usual limitations of a surrogate must be borne in mind, in particular the difficulty in reliably predicting the magnitude of natalizumab's effect at two years. Completion of the ongoing studies is essential to the verification of the safety and efficacy observed at one year.

Accelerated approval requires that the new drug provide evidence of the potential to address an unmet medical need. Many MS patients continue to have exacerbations while taking one of the available first-line MS therapies. None of the currently available therapies have proven efficacy when used as an add-on therapy. Study 1802 provides evidence that natalizumab is effective as an add-on therapy for subjects who continue to have relapses while on a first-line therapy (Interferon  $\beta$ -1a). Therefore, natalizumab has the potential to address an unmet medical need.

The clinical review recommendation is for accelerated approval of natalizumab for the treatment of patients with relapsing forms of MS, to reduce the frequency of clinical exacerbations.

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## **1.2 Recommendation on Postmarketing Actions**

### **1.2.1 Risk Management Activity**

No specific risk management activities are recommended for the marketing of natalizumab.

### **1.2.2 Required Phase 4 Commitments**

1. To conduct a pharmacokinetic study of at least 6 months duration to assess whether chronic administration of natalizumab in combination with glatiramer acetate results in a drug interaction that suggests the need for a dose adjustment of natalizumab.
- 2.
3. To verify that the clinical benefit of reduction in exacerbations is sustained with continued natalizumab administration. This will be accomplished by completing the ongoing studies C-1801 and C-1802 through the planned two years and submitting the results along with appropriate labeling changes.
4. To further evaluate the safety of natalizumab and the efficacy of natalizumab on physical disability. This will be accomplished by completing the ongoing 2-year studies (C-1801 and C-1802) and submitting the study results, including all safety and efficacy data, for all study subjects through Week 128 or subject withdrawal. Appropriate labeling changes will be proposed as part of this submission.
5. To conduct a concurrently controlled pregnancy registry for women who become pregnant while exposed to natalizumab, to identify the pregnancy outcomes and postnatal health status of the children. This commitment includes submitting a revision to the label, once the design of the registry is finalized, that informs patients and physicians of the existence of the registry.
6. To conduct a study to measure the effects of at least a six-month course of natalizumab on immune responses in subjects with relapsing forms of MS that evaluates the effect of natalizumab on percentages of lymphocytes including CD3+, CD4+, CD8+, as well as B and NK cells, and the associated  $\alpha$ 4-integrin expression and binding site saturation.
7. To conduct a study of the effect of natalizumab on neoantigen immunization with respect to interval from dosing and the potential for induction of tolerance and assessment of tolerance using a series of two booster immunizations post-natalizumab clearance. If such a study provides evidence that natalizumab has an effect on neoantigen immunization, the applicant commits to conducting a study of the effect of natalizumab on patient response to a neovaccination after withdrawal of natalizumab treatment.

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8. To conduct a study of the effect of natalizumab on recall antigen responses in a chronic dosing situation, including the levels of antibody to the recall antigen and the ability of a booster immunization to raise antibody levels.
9. To use new binding and neutralizing assays to conduct a study of the development and general time course of immunogenicity at any level of titer, and the relationship of natalizumab immunogenicity to safety events.
10. Pending the development of a new assay for antibodies to natalizumab, to use the current assay to assess the immunogenicity of natalizumab by conducting a study of patients who are at least three months post-treatment, so that no natalizumab is present in serum to interfere with the assay. The applicant will analyze these immunogenicity data with consideration of the reasons for discontinuing natalizumab and the adverse event profile of the subjects.

#### 1.2.3 Other Phase 4 Requests

There are no additional requests for clinical Phase 4 studies.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

Natalizumab is a monoclonal antibody for intravenous (IV) administration. Natalizumab binds to a human integrin that is highly expressed on the surface of white blood cells. Natalizumab may produce its clinical effect in MS by interfering with the movement of inflammatory white blood cells from the blood vessels into the brain and spinal cord.

The applicant has studied natalizumab for the treatment of relapsing MS and Crohn's disease (CD). Studies in CD are ongoing. This application is for the treatment of MS, to decrease the frequency of relapses. Studies 1801 and 1802, the two pivotal efficacy and safety trials, randomized 942 and 1171 subjects, respectively, to receive either natalizumab or placebo for up to 28 months. The safety review considers a database of 1617 MS patients who have been exposed to natalizumab for a median duration of 20 months.

#### 1.3.2 Efficacy

Studies 1801 and 1802 are the two Phase 3, multicenter, randomized, double-blind, placebo-controlled studies that provide the primary evidence of effectiveness for natalizumab in MS, and are the focus of this review. Both studies enrolled patients who experienced at least one clinical relapse during the prior year, thereby providing evidence of active disease. For each study, the primary endpoint was the annualized relapse rate at one year, comparing the natalizumab group to the placebo group.

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Study 1801 enrolled primarily patients who had never received any interferon beta or glatiramer acetate. Patients were randomized 2:1 to receive natalizumab (n=627) or placebo (n=315) every four weeks for up to 28 months. Study subjects who received natalizumab experienced an annualized relapse rate of 0.25 relapses/patient-year, compared to 0.74 relapses/patient-year in the placebo group (p<0.001). This represents a relative reduction of 66%.

Study 1802 was an "add on" study that enrolled patients who had experienced one or more relapses despite treatment with Avonex<sup>®</sup> (Interferon  $\beta$ -1a) during the year prior to study entry. Patients were randomized (1:1) to receive natalizumab (n=589) or placebo (n=582) every four weeks for up to 28 months. All patients continued to receive Avonex<sup>®</sup> throughout the study. Subjects who received natalizumab and Avonex<sup>®</sup> experienced an annualized relapse rate of 0.36 relapses/patient-year, compared to 0.78 relapses/patient-year in the placebo group (p<0.001). This represents a relative reduction of 54%.

In both Phase 3 studies, the three prespecified secondary endpoints at one year were the increase in the proportion of relapse-free subjects, the reduction in the number of new or newly enlarging T2 lesions on brain magnetic resonance imaging (MRI), and the reduction in the number of gadolinium-enhancing lesions on brain MRI. Natalizumab administration was associated with a statistically persuasive effect on each of these endpoints in both Phase 3 studies. In both studies, the salutary effects of natalizumab were also consistent across the major subgroups.

The decrease in relapse rate associated with natalizumab alone (Study 1801) is approximately twice the magnitude of the effect observed with registration trials for the currently available first-line therapies (Avonex<sup>®</sup>, Betaseron<sup>®</sup>, Copaxone<sup>®</sup>, and Rebif<sup>®</sup>) for the proposed indication. Natalizumab is the first drug to show efficacy when used as an add-on to a current first-line therapy (Study 1802). The final results of the ongoing two-year studies will be necessary to verify the efficacy of natalizumab. There are no studies providing a direct comparison of natalizumab to any of the current first-line therapies.

### 1.3.3 Safety

A total of 1617 MS patients, in both controlled and uncontrolled studies, have been exposed to natalizumab, with a median duration of exposure of 20 months. Natalizumab appears to cause hypersensitivity reactions, an increased risk of some infections, headache, depression, joint pain, and menstrual disorders. Hypersensitivity reactions are strongly associated with the development of antibodies to natalizumab. The infections were predominately mild respiratory tract infections, influenza, and urinary tract infections. Serious adverse events were uncommon. In Study 1801, the most frequent serious adverse events associated with natalizumab were infections (2.1% versus 1.3% with placebo, including pneumonia [0.6%]), hypersensitivity reactions (1.3%, including anaphylaxis/anaphylactoid reaction [0.8%]), depression (0.8%, including suicidal ideation, [0.5%]), and cholelithiasis (0.8%). Natalizumab's overall safety profile was similar in Studies 1801 and 1802, and appears favorable compared to the currently available first-line MS therapies (Avonex<sup>®</sup>, Betaseron<sup>®</sup>, Copaxone<sup>®</sup>, and Rebif<sup>®</sup>). However, there are no studies that provide a direct comparison of the safety of natalizumab to any of the current first-line therapies. Review

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of the final results of the ongoing two-year studies, along with postmarketing experience, will be necessary to better characterize the safety of natalizumab.

#### 1.3.4 Dosing Regimen and Administration

The recommended dose of natalizumab is 300 milligrams by IV infusion every four weeks. Patients should be observed during the infusion and for one hour after the infusion is complete. The infusion should be discontinued if there are any signs or symptoms suggestive of a hypersensitivity reaction. These signs and symptoms include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain.

#### 1.3.5 Drug-Drug Interactions

After multiple dosing, Interferon  $\beta$ -1a (Avonex<sup>®</sup> 30 mcg IM once weekly) reduced the clearance of natalizumab by 30%. Although serum natalizumab levels would be expected to increase with co-administration of Interferon  $\beta$ -1a, the similarity of the natalizumab-associated adverse event profile between Study 1801 (in the absence of Interferon  $\beta$ -1a) and Study 1802 (with co-administered Interferon  $\beta$ -1a) suggests that co-administration of an interferon does not necessitate a change in the natalizumab dose to maintain safety.

Results of studies in MS patients taking natalizumab and concomitant interferon  $\beta$ -1a or glatiramer acetate are inconclusive with regard to the need to adjust the dose of interferon or glatiramer acetate.

#### 1.3.6 Special Populations

The safety and efficacy of natalizumab have not been adequately studied in patients with chronic progressive MS, renal insufficiency, hepatic insufficiency, age  $\geq 65$ , age  $< 18$ , or in women who are pregnant or nursing. Considering the low incidence of MS below age 16, the studies necessary to demonstrate safety and efficacy in a pediatric population would be highly impractical. Therefore, FDA approved the applicant's request for a waiver of the requirement to perform studies in the pediatric population. Natalizumab should be used during pregnancy only if clearly needed.



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## 2 INTRODUCTION AND BACKGROUND

Multiple sclerosis is a chronic, inflammatory, possibly autoimmune, demyelinating disease of the central nervous system. Multiple sclerosis is a common cause of neurological disability in young adults, primarily affecting people between 20 and 40 years of age, and affecting women approximately twice as often as men. The disease affects approximately 300,000 patients in the US, with an annual incidence of approximately 1 to 5 per 100,000 (National MS Society).

Experts in the field generally recognize three clinical forms of MS: relapsing-remitting, secondary progressive, and primary progressive (Lublin and Reingold, 1996). Relapsing-remitting MS is the presenting form in up to an estimated 80 to 85% of patients, and involves recurrent attacks of neurological symptoms and signs (relapses or exacerbations) involving multiple areas of the nervous system. Attacks occur at variable time intervals, ranging from months to years apart. These exacerbations or relapses are followed by variable degrees of recovery (remissions). The majority of subjects with RRMS develop secondary progressive MS (SPMS) in which periods of stable recovery give way to neurological decline over time. About 50% of patients with RRMS will develop SPMS within 10 years of onset; the proportion approaches 80% after 25 years (Runmarker and Anderson, 1993).

The predominant tool used to measure the accumulation of disability is the expanded disability scale score (EDSS), which is determined by assessing the Kurtzke Functional Systems in each of 6 neurological areas (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, and visual). EDSS scores range from 0 (normal) to 10 (death) in 1/2-unit steps. Patients are fully ambulatory through EDSS 4.5, after which progressive impairment in ambulation becomes the predominating factor in the EDSS.

Diagnosis, especially for inclusion in clinical trials, has been codified over the years by consensus of the field, and published as formalized criteria and categories (Poser et. al., 1983). Diagnosis generally requires confirming at least two lesions, which must have occurred in different parts of the CNS and at different times (demonstrating dissemination of disease activity in both time and space). "T1-weighted" MRI performed after the infusion of gadolinium (Gd) is believed to show cranial lesions of acute onset, the contrast agent leaking through the normally impermeable endothelial barrier. These lesions may resolve over a period of months. "T2-weighted" MRI lesions are believed to represent fixed, residual pathology. Magnetic resonance imaging has become a standard procedure in the diagnosis of MS. Magnetic resonance imaging demonstrates the MS lesions scattered throughout the brain. While MRI lesions are not pathognomonic for MS, the pattern of lesions can be strongly suggestive. More recently, diagnostic criteria that place additional emphasis on MRI imaging (McDonald et. al., 2001) have become popular to define the MS population for clinical trials.

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## 2.1 Product Information

Natalizumab is a recombinant humanized IgG4 $\kappa$  antibody produced in murine myeloma cells. Natalizumab binds to the  $\alpha$ 4-subunit of the  $\alpha$ 4 $\beta$ 1 human integrin (also known as VLA-4), which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Natalizumab is a new biological entity that blocks the interaction of the integrin with vascular cell adhesion molecule-1 (VCAM-1), additional ligands such as osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab also blocks the interaction of  $\alpha$ 4 $\beta$ 7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions inhibits migration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. Natalizumab may also suppress inflammatory reactions in diseased tissues by inhibiting the interaction of  $\alpha$ 4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. Therefore, natalizumab may suppress inflammatory activity at the disease site and inhibit migration of additional immune cells to inflamed tissues.

Natalizumab is formulated as a solution. Each 15 mL dose contains 300 mg natalizumab; 123 mg sodium chloride, USP; 17.0 mg sodium phosphate, monobasic, monohydrate, USP; 7.24 mg sodium phosphate, dibasic, heptahydrate, USP; 3.0 mg polysorbate 80, USP/NF, in water for injection, USP at pH 6.1. Natalizumab is supplied as a sterile, colorless, clear to slightly opalescent concentrate for IV infusion.

Biogen Idec and Elan Pharmaceuticals have been partners in the development of natalizumab as a treatment for MS. However, Biogen Idec is the specified applicant for this submission.

Clinical scale lots of natalizumab were used in the two Phase 3 clinical trials (1801 and 1802) that form the primary support for this application. However, only one modestly-sized clinical trial (1803) has included administration of the commercial scale natalizumab that the sponsor proposes to market for the treatment of MS (see Section 4.1, Sources of Clinical Data, and Section 2.5.5, New Commercial Material, of this review and Dr. Elena Gubina's CMC review of this application).

Natalizumab's proposed trade name is Tysabri. In the medical literature, this product has been referred to as either natalizumab or Antegren.

The applicant proposes that natalizumab be indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations.

The applicant's proposed recommended dose of Natalizumab is 300 mg IV infusion,

The applicant states that the safety and effectiveness of Natalizumab have not been adequately studied in pregnant women, nursing mothers, patients aged 65 years and older, and patients below the age of 18.



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## 2.2 Currently Available Treatment for MS

MS therapies can be broadly divided into two categories: those directed against the immune system and intended to inhibit the disease process, and those intended to reduce symptoms. In general, the former have been less successful than the latter; however, it is immune modulator approaches that are likely to provide major advances in effective therapy.

### 2.2.1 Immune Modulators Approved for Treatment of MS

There are currently five drugs approved in the United States for treatment of MS. Betaseron® (Interferon  $\beta$ -1b), Avonex® (Interferon  $\beta$ -1a), and Rebif® (Interferon  $\beta$ -1a), are interferons licensed for the treatment of relapsing forms of MS. Copaxone® (glatiramer acetate) is a non-interferon licensed for RRMS. Betaseron® is indicated for use in ambulatory RRMS patients to reduce the frequency of clinical exacerbations. Avonex® is indicated for the treatment of relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Rebif® is indicated for the treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Copaxone® is indicated for reduction of the frequency of relapses in patients with relapsing-remitting MS. These four products are the first and second-line treatments for MS, and each is administered by subcutaneous or intramuscular injection. Novantrone® (Mitoxantrone), a cancer chemotherapeutic agent, was approved in 2000 for patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS. Due largely to its cumulative dose-limiting cardiotoxicity, Novantrone® has been used in only a very small proportion of the MS population.

In clinical use, the interferon betas and glatiramer acetate have a variety of adverse effects, which vary for the different products. These adverse effects include injection site reactions, flu-like symptoms, fever, chills, headache, fatigue, asthenia, myalgia, and anorexia. Hematological (lymphopenia, neutropenia, thrombocytopenia, and anemia) and hepatic toxicities are known side-effects of interferon beta therapy. There is also concern because of the potential for interferon betas to cause depression.

It is estimated that approximately 350,000 patients globally are currently receiving treatment with one of the approved MS therapies (applicant's internal data). However, despite the demonstrated efficacy of these treatments and their widespread use, there is a substantial population of patients with relapsing MS who remain untreated for their disease. Many of these patients have disease with relatively little evidence of active inflammation clinically (relapses) or by MRI, and therefore choose not to begin treatment. Some patients have active relapsing MS but choose not to be treated because of fear of self-injection or potential adverse effects from the available treatments. Other patients have tried an existing therapy but discontinued treatment due to intolerance, adverse effects, or lack of efficacy.

Of those patients who do receive treatment, a substantial number continue to experience disease activity clinically and on MRI. This ongoing disease activity is expected because each of the approved medications produces only approximately a 30% reduction in relapse rate (Interferon

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Study Group 1993, Jacobs et al, 1996; PRISMS Study Group, 1998; Johnson et al, 1995). Therefore, a substantial unmet medical need exists for MS treatments that offer more efficacy and are well-tolerated.

Although a variety of therapeutic strategies are widely used in clinical practice to manage continued disease activity while on treatment (e.g., switching therapy, changing dose and frequency of interferon, various combination treatments), these practices are largely empirical as there are no randomized, controlled trials to assess the efficacy or safety of these approaches. Therefore, there also exists a substantial unmet medical need for therapies that can be added to existing therapies to improve efficacy.

#### 2.2.2 Other Immune Modulators and Immunosuppressants

Corticosteroids are used for treatment of acute exacerbations. Steroids can decrease the peak severity and duration of the acute exacerbations, but have not been proven to decrease the frequency of relapses or prevent the long term progression of disability.

Other immunosuppressants (e.g., azathioprine, cyclophosphamide, and methotrexate) have been studied for treatment of MS. However, their limited benefit and potential for significant side effects have prevented widespread use for MS.

Intravenous immunoglobulin (IVIG) infusions are believed by some investigators to be effective in treating MS, but are not widely used in the U.S., and do not have an approved indication for the treatment of MS.

#### 2.2.3 Symptomatic Therapies

Numerous agents have been used for symptomatic benefit in MS. These include amantadine and pemoline for treatment of fatigue, baclofen (a muscle relaxant and antispasmodic), tizanidine and benzodiazepines to treat spasticity, urologic antispasmodics for bladder dysfunction, and a number of agents for neuropsychologic impairment and pain management, including benzodiazepines, antidepressants, and anticonvulsants. None of these agents slow the progression of the disease or influence the frequency of relapses.

### 2.3 Availability of Proposed Active Ingredient in the United States

Natalizumab is a new molecular entity that is not currently marketed in the United States.

### 2.4 Important Issues With Pharmacologically Related Products

Currently, no pharmacologically-related products are marketed. Accordingly, it is not possible to draw upon experience from pharmacologically related products.

Natalizumab is an immune-modulating agent; therefore, safety concerns include the potential for increased risks of infection and/or malignancy. Natalizumab is a biologic; therefore,

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immunogenicity is a concern. Safety issues of infection, malignancy, and immunogenicity are discussed in Section 7 of this review.

Natalizumab is an IgG4 antibody that exists in two forms, as a bivalent antibody (two heavy chains and two light chains) and a monovalent antibody (one heavy chain and one light chain). Two formulations of natalizumab with differences in the proportion of bivalent versus monovalent antibody were found to be comparable in a clinical bioequivalence study (see CMC Review by Drs. Gubina, Kutza, and Zhang, and Clinical Pharmacology review by Dr. Mahmood). Theoretically, the monovalent natalizumab antibody may engage in scrambling with monovalent IgG4 antibodies to other antigens. Scrambling is the physical association of two monovalent IgG4 antibodies to different antigens to produce a functional bispecific antibody (Aalberse and Schuurman, Immunology, 2002). However, natalizumab administration in combination with other immunogenic MS therapies, including glatiramer acetate and all three currently approved beta-interferons, may provide an opportunity for scrambling between natalizumab monovalent antibodies and any IgG4 antibodies formed to the concomitant MS therapy. Particularly, antibodies to glatiramer acetate are primarily of the IgG4 type. However, the potential differential activity of natalizumab bivalent vs. monovalent antibody and the potential for natalizumab monovalent antibody to scramble with other monovalent IgG4 antibodies are theoretical concerns with unclear clinical implications. For additional discussion of these issues, see Dr. Lei Zhang's CMC review of this application.

## 2.5 Presubmission Regulatory Activity

### 2.5.1 Fixed Dosing Regimen

Natalizumab was administered using weight-adjusted dosing in Phase 1 and Phase 2 clinical trials in MS. Clinical trials later in the course of development, including the pivotal studies 1801 and 1802, used fixed dosing of natalizumab 300 mg IV every 4 weeks (see Section 4.1, Sources of Clinical Data). In a December 10, 2001 letter to the IND sponsor, FDA noted the change from weight-adjusted dosing to a fixed dose and advised the sponsor, "If this study [C-1801] or subsequent studies provide evidence that weight may influence either the safety or the efficacy of Natalizumab, then it may be necessary for you to obtain additional pharmacokinetic/pharmacodynamic data regarding Natalizumab, and/or conduct additional studies of the safety and efficacy of weight-adjusted dosing of Natalizumab for patients with multiple sclerosis." Explorations of natalizumab's efficacy and safety with respect to subject weight are a focus of this review.

### 2.5.2 Interaction of Natalizumab with Standard MS therapies

In a December 10, 2001 letter to the sponsor, FDA also expressed concern regarding the interaction of any new MS therapy with the standard MS therapies: "Substantial pharmacokinetic, pharmacodynamic, and safety data on the interaction of a potential new treatment with available standard therapies will be necessary in a license application." Largely

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as a result of this advice, the add-on study with Avonex<sup>®</sup> (Study 1802) was designed and carried out.

#### 2.5.3 Pediatric Waiver

On May 1, 2002, the applicant requested a pediatric waiver pursuant to 21 CFR 601.27(c). The FDA considered the low incidence of MS below age 16 and accepted the sponsor's certification that the studies necessary to demonstrate safety and efficacy in a pediatric population would be highly impractical. The FDA decision to approve the applicant's request was consistent with FDA precedent regarding other therapies for MS and was conveyed to the applicant in an August 2, 2002 letter.

#### 2.5.4 Application for Accelerated Approval

The applicant has sponsored two ongoing Phase 3, randomized, double-blind, placebo-controlled studies (C-1801 and C-1802) which provide the primary basis for this license application (see Section 4.1, Sources of Clinical Data). Each Phase 3 study includes administration of natalizumab to MS subjects for up to 28 months. However, the IND sponsor pre-specified an analysis at approximately one year (see Section 6.1.3, Study Design, and Dr. Kallappa Koti's review of this application for a discussion of the timing of the "one-year" analysis) and pre-specified a primary endpoint based on the effect on relapse rate at the one-year analysis.

In review of previous applications for the treatment of MS, FDA has required data through two years of drug administration to support an indication for decreasing the frequency of clinical relapse (see review memorandum of Dr. Marc Walton). The applicant has applied for accelerated approval (see Guidance for Industry, Fast Track Drug Development Programs – Designation, Development, and Application Review, Center for Drug Evaluation and Research, July, 2004) based on data on the safety and efficacy of natalizumab through approximately one year of administration. The sponsor's basis for consideration of accelerated approval is the demonstration of an effect that addresses an unmet medical need, specifically the demonstration of clinical benefit when the agent is administered as add-on therapy to one of the currently approved agents (see Section 2.2.1, Immune Modulators Approved for Treatment of MS). To grant a license under accelerated approval, the FDA must also deem the one-year data as reasonably likely to predict a clinical benefit at two years. In effect, under accelerated approval, the effect on relapses at one year would serve as a surrogate for an effect on relapses at two years.

During a February 17, 2004 pre-BLA meeting, FDA agreed with the sponsor that, given the apparent magnitude of the treatment effect at one year, there was the potential for the data to serve as a surrogate for benefit at two years. The FDA also agreed that the potential to show benefit at two years, in combination with evidence suggesting that natalizumab addresses an unmet medical need, could support an application for accelerated approval (see review memorandum of Dr. Marc Walton).

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#### 2.5.5 New Commercial Material

During a February 17, 2004 pre-BLA meeting, FDA asked the sponsor to submit "data with regard to the comparability of the new commercial-scale product and the product used in the Phase 2 and Phase 3 clinical trials." For further discussion of this issue, see Section 2.1, Product Information, of this review, the CMC Review by Drs. Elena Gubina, Joseph Kutza, and Lei Zhang, and the Clinical Pharmacology review by Dr. Mahmood.

#### 2.6 Other Relevant Background Information

Neither natalizumab nor any other anti-integrin is currently marketed anywhere in the world.

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

The CMC Review concludes that the manufacture of natalizumab is well controlled and leads to a product that is pure and potent. However, there are limitations of the current assay for detection of antibodies to natalizumab. See CMC review by Drs. Gubina, Kutza, and Zhang, and Section 7.1.10, Immunogenicity, of this review.

#### 3.2 Animal Pharmacology/Toxicology

The non-clinical toxicology review concludes that natalizumab is generally well tolerated in the animal models studied. The toxicities observed in animals were primarily extensions of the known pharmacologic activity of the drug. Non-clinical reproductive toxicology studies demonstrated that treatment with natalizumab has the potential to reduce fertility. See the Non-clinical Toxicology review by Dr. Barbara Wilcox.

The non-clinical pharmacology review concludes that toxicities of natalizumab in the reviewed pharmacology studies were limited to increases in circulating total leukocytes and differential lymphocyte, monocyte, eosinophil, and basophil counts. See the Non-clinical Pharmacology review by Dr. Anne Pilaro.

### 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

#### 4.1 Sources of Clinical Data

This review is based on data from clinical trials conducted by the applicant, Biogen Idec, in partnership with Elan Pharmaceuticals.

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<u>Significant Submission(s) Reviewed</u>		<u>Document Date</u>
STN 125104/0	Original Submission	28-May-2004
STN 125104/0.001	Study 1803 Report Update	22-Jun-2004
STN 125104/0.002	Study 1803 Final Report	29-Jul-2004
STN 125104/0.003	Response to Clinical Information Request	03-Aug-2004
STN 125104/0.007	Response to Clinical Information Request	10-Sept-2004
STN 125104/0.011	Response to Clinical Information Request	21-Sept-2004
STN 125104/0.012	120-Day Safety Update	22-Sept-2004
STN 125104/0.027	Response to Clinical Information Request	05-Nov-2004
STN 125104/0.028	Revised Package Insert	05-Nov-2004
STN 125104/0.031	Response to Clinical Information Request	15-Nov-2004
STN 125104/0.032	Response to Clinical Information Request	15-Nov-2004
STN 125104/0.033	Response to Clinical Information Request	15-Nov-2004
STN 125104/0.034	Response to Clinical Information Request	15-Nov-2004
STN 125104/0.036	Response to Clinical Information Request	16-Nov-2004

## 4.2 Tables of Clinical Studies

Natalizumab is being co-developed by Biogen Idec and Elan Pharmaceuticals for the treatment of RRMS and moderate to severe active CD. Table 1 summarizes the clinical trials initiated as part of development for the MS indication. The clinical trials in MS form the primary basis for this review. Clinical trials in CD and ulcerative colitis are described briefly in Table 2; however, they did not contribute materially to the evidence of effectiveness or safety for natalizumab in MS, and the data were considered primarily in terms of more serious safety events.

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**Table 1: Clinical Development in Multiple Sclerosis**

Study #	Goals	Population	Design	# of Doses	N	Natalizumab Dose	Result
<b>Phase 1</b>							
101	Safety, tolerability	Male normal volunteers	RD, DB, PC, DE	1	35	0.03 - 3.0 mg/kg	Tolerated
201	Safety, tolerability	RRMS, SPMS	RD, DB, PC, DE	1	25	0.03 - 3.0 mg/kg	Tolerated
224	Safety, PK	MS subjects receiving a beta-interferon	Open-label	1	38	3 and 6 mg/kg	Tolerated
225	PK, PD	RRMS, SPMS	RD, DB, PC, DE	1	38	3 and 6 mg/kg	Tolerated
<b>Phase 2</b>							
201	Preliminary efficacy - MRI	RRMS, SPMS	RD, DB, PC, 24-week duration	2	73	3 mg/kg	+ MRI
202	Preliminary efficacy - EDSS, relapses	RRMS, SPMS	RD, DB, PC, 24-week duration	2	36	3 and 6 mg/kg	+ MRI, - EDSS, + relapses
231	Preliminary efficacy - MRI, EDSS, relapses	RRMS, SPMS	RD (1:1:1), DB, PC, DE, 6-month duration	6	213	3 and 6 mg/kg	+ MRI, - EDSS, + relapses
<b>Phase 3</b>							
1801	Confirmatory efficacy and safety - relapses, EDSS	RRMS	RD (1:1:1), DB, PC, 2-year duration	30	942	300 mg	See below
1802	Confirmatory efficacy and safety - relapses, EDSS	RRMS patients receiving a beta interferon	RD (1:1:1), DB, PC, 2-year duration	30	1196	300 mg	See below
<b>Additional Clinical Trials</b>							
1803	PK interaction	RRMS patients receiving glatiramer acetate	RD (1:1:1), DB, PC, 6-month duration	6	110	300 mg	No PK/PD interaction
1804	Emergency use	5 y.o. girl, refractory MS	Open-label	10 (of 18 planned)	1	3 - 6 mg/kg	Died 5 months after discontinuing natalizumab
1805	Bioequivalence, compare formulations	Normal volunteers	Crossover	2	88	300 mg	Bioequivalent
1806	Bioequivalence, compare formulations	Normal volunteers	Crossover	2	86	300 mg	Bioequivalent
1808	Extension efficacy and safety	1801, 1802, 1803 completers	Open-label	Up to 24	124 (as of 12/2/04)	300 mg	Pending

RD = Randomized; DB = double-blind; PC = placebo-controlled; DE = dose-escalation;  
 PK = Pharmacokinetics; PD = Pharmacodynamics

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**Table 2: Clinical Development in CD and Ulcerative Colitis (UC)**

Study #	Goals	Population	Design	# of Doses	N	Natalizumab Dose
<b>Phase 1</b>						
CD201	Preliminary safety and efficacy	CD	RD, DB, PC	1	30	3 mg/kg
<b>Phase 2</b>						
CD202	Dose-escalation; preliminary safety and efficacy	CD	RD, DB, PC	1 to 2	244	3 and 6 mg/kg
CD251	Safety, tolerability	CD	Open-label	2	96	6 mg/kg
CD303	Safety, tolerability, PK	Adolescents with CD	Open-label	1	66	3 mg/kg
CD352	Safety, tolerability	Adolescents with CD	Open-label	Up to 24	26	3 mg/kg
CD306	Safety, tolerability	CD subtypes receiving infliximab	RD, DB, PC	3	79	3 mg/kg
<b>Phase 3</b>						
CD301	Confirmatory efficacy and safety	Moderate to severe CD	RD, DB, PC	3	904	300 mg
CD303	Confirmatory efficacy and safety	CD patients with initial response to CD301	RD, DB, PC	Up to 2	426	300 mg
CD351	Extension efficacy and safety	CD251, CD301, CD303, CD306 completers	Open-label	Up to 24	589	300 mg
<b>Additional Clinical Trials</b>						
CD201	Preliminary safety and efficacy	UC	Open-label	1	10	3 mg/kg

RD = Randomized; DB = double-blind; PC = placebo-controlled; DE = dose-escalation; PK = Pharmacokinetics

### 4.3 Review Strategy

The primary focus of the efficacy review is the two Phase 3 studies in MS, Studies 1801 and 1802. These two studies are the only large, placebo-controlled studies of the efficacy of natalizumab at the proposed recommended dose, in the proposed target population. Both studies provide data through an average of one year. Study 231 (see Section 10.1.1, Study 231) was a randomized, double-blind, placebo-controlled study in MS, but used weight-adjusted dosing rather than the proposed recommended fixed dose, and administered a total of only 6 doses of study agent to each subject over 20 weeks. Study 231 was well-designed and was reviewed for evidence supportive of clinical efficacy.

The safety review is also based primarily on Studies 1801 and 1802, which provide the only placebo-controlled data in MS subjects who received the proposed recommended dose of



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natalizumab for more than 6 months. Other MS studies and studies in other indications were reviewed for safety signals and included in an integrated summary of safety. However, almost all of these studies were limited in size, uncontrolled, or did not include exposure of subjects to the proposed recommended fixed dose of natalizumab for more than 6 months. Therefore, the design of these studies substantially limited their informativeness with regard to product safety. The major exception to these design limitations is CD303, a relatively large, randomized, double-blind, placebo-controlled study of the proposed recommended fixed dose of natalizumab administered to subjects with CD for up to 12 months. However, CD303 was ongoing at the time of this license application, and did not contribute substantially to the safety database.

Studies 1802 and 1803 were reviewed for evidence of an interaction between natalizumab and current standard therapies, a beta-interferon (1802) or glatiramer acetate (1803).

#### **4.4 Data Quality and Integrity**

The Division of Scientific Investigations conducted Bioresearch Monitoring Inspection (BIMO) audits of three study sites. Each site was selected because it enrolled a relatively large number of subjects into a proposed pivotal trial, either 1801 (Site #108), 1802 (Site #168), or 1801 and 1802 (site #125). These sites were also selected because their North American locations made them more accessible for audit than comparable sites on other continents. The BIMO clinical inspectors concluded that the data submitted in the BLA, as represented by these three sites, were valid and reliable.

#### **4.5 Compliance with Good Clinical Practices**

The investigators for both Study 1801 and Study 1802 obtained Ethics Committee (EC) and/or Institutional Review Board (IRB) approval for the protocol and written informed consents for subjects, in conformance with the International Conference on Harmonization (ICH) Tripartite Guideline on Good Clinical Practices (GCP), and/or 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312. Investigational sites in Europe, Australia, Canada, New Zealand, Israel, Switzerland, and Turkey also conformed to local practice and regulations. Prior to any participation in Study 1801 or 1802, each subject provided written informed consent in accordance with local practice and regulations.

During the course of Study 1802, the sponsor closed a single site in \_\_\_\_\_ due to protocol noncompliance. The sponsor excluded data from this site, which enrolled 25 subjects, from all efficacy analyses. However, the Center for Drugs Evaluation and Research (CDER) conducted sensitivity analyses to assess the impact of excluding this site on the study efficacy results (see Section 6.1.4.5.2.1, Exploration of Irregularities). Safety data from the site were included in the safety analyses.

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#### 4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry (Financial Disclosure by Clinical Investigators, CDER, March 20, 2001). Disclosable arrangements that might represent a conflict of interest and bias the investigator occurred in the two pivotal MS studies (Study 1801: sites 109, 110, 119, 125, and 730; Study 1802: sites 125, 144, 148, 158, 160, 176, 183, 197, 451, 465, 656, and 752). Studies 1801 and 1802 were double-blind studies designed to reduce the potential for investigators' bias to influence study results. CDER conducted sensitivity analyses to assess the potential impact of investigator bias at these sites (see Section 6.1.4.5.2.2, Financial conflicts of interest).

### 5 CLINICAL PHARMACOLOGY

Natalizumab binds to the  $\alpha 4 \beta 1$  integrin expressed on the surface of all leukocytes except neutrophils and blocks the interaction with the integrin's receptors. The receptors for the  $\alpha 4$  family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium and the mucosal addressin cell adhesion molecule-1 (MadCAM-1) present on mucosal endothelial cells. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. *In vitro*, natalizumab also blocks  $\alpha 4$ -mediated cell binding to ligands such as osteopontin and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). *In vivo*, natalizumab may further act to inhibit the interaction of  $\alpha 4$ -expressing leukocytes with their ligand(s) in the extracellular matrix and on parenchymal cells, thereby inhibiting further recruitment and inflammatory activity of activated immune cells.

The specific mechanism(s) by which natalizumab exerts its effect(s) in multiple sclerosis have not been fully elucidated. In multiple sclerosis, lesions are believed to occur when activated inflammatory cells, including T-lymphocytes, cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and their counter-receptors present on vascular endothelial cells. The clinical effect of natalizumab in multiple sclerosis may be secondary to blockade of the molecular interaction of  $\alpha 4 \beta 1$ -integrin expressed by inflammatory cells with VCAM-1 on vascular endothelial cells, and with CS-1 and/or osteopontin expressed by parenchymal cells in the brain.

For additional discussion of the clinical pharmacology of natalizumab, see Dr. Iftekhhar Mahmood's Clinical Pharmacology review of this application.

#### 5.1 Pharmacokinetics

Following the repeat IV administration of a 300 mg dose of natalizumab to MS patients, the mean maximum observed serum concentration was  $98 \pm 34$   $\mu\text{g/mL}$ . Mean average steady-state natalizumab concentrations over the dosing period were approximately 30  $\mu\text{g/mL}$ . The mean

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half-life of  $11 \pm 4$  days was observed with a clearance of  $16 \pm 5$  mL/hour. The distribution volume of  $5.7 \pm 1.9$  L was consistent with plasma volume.

With co-administration of Avonex® (Interferon  $\beta$ -1a) 30  $\mu$ g IM once weekly, natalizumab clearance decreased by 30% and half-life increased by 30% following the sixth dose (at Week 20) of natalizumab as compared to the first dose.

Results of studies in MS patients taking natalizumab and concomitant beta interferon (Avonex® 30  $\mu$ g IM once weekly) or glatiramer acetate (Copaxone® 20 mg subcutaneous [SC] daily) are inconclusive with regard to the need for dose adjustment of beta interferon or glatiramer acetate.

In normal volunteers and in patients with MS, the  $C_{max}$  increased with the natalizumab dose and was linear between doses of 0.3 and 3 mg/kg. However, the area under the concentration time curve (AUC) did not increase proportionally with dose, and the clearance of natalizumab decreased with increasing dose. Therefore, the overall pharmacokinetics of natalizumab are nonlinear between doses of 0.3 and 3 mg/kg. Following a 300 mg fixed dose of natalizumab given every 4 weeks to patients with MS,  $C_{max}$ , half-life and  $AUC_{(0-\infty)}$  were comparable between the first and the sixth dose.

Pharmacokinetics of natalizumab in pediatric multiple sclerosis patients or those with renal or hepatic insufficiency have not been studied.

For additional discussion of natalizumab pharmacokinetics, including bioequivalence studies 1805 and 1806, see Dr. Iftekhar Mahmood's Clinical Pharmacology review of this application.

## 5.2 Pharmacodynamics

Natalizumab administration increases the number of circulating leukocytes (including lymphocytes monocytes, basophils, and eosinophils), due to inhibition of transmigration out of the vascular space. Increases in circulating leukocytes are maintained throughout the administration period; counts return to baseline levels when natalizumab is discontinued. Natalizumab does not affect the number of circulating neutrophils.

The available data are insufficient to assess whether antibodies to natalizumab have any impact on the pharmacokinetics of natalizumab (see Section 7.1.10, Immunogenicity).

For additional discussion of natalizumab pharmacodynamics, see Dr. Iftekhar Mahmood's Clinical Pharmacology review of this application.

## 5.3 Exposure-Response Relationships

Based on a pharmacodynamic model, natalizumab serum concentrations of approximately 2.5 – 3  $\mu$ g/mL would be required to maintain a minimum  $\alpha$ 4-integrin saturation of 80%. In Study 231, approximately 90% of subjects in both dose groups (3 mg/kg and 6 mg/kg) had natalizumab

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serum concentrations in excess of 2.5 mcg/mL four weeks following the last infusion. Studies 231 and CD202 provide evidence of no relationship between body weight and clearance. Also, both weight-adjusted doses administered in Study 231 resulted in similar activity, safety, and tolerability. Therefore, the sponsor abandoned weight-adjusted dosing, as administered in the Phase 1 and Phase 2 studies (see Section 4.2, Tables of Clinical Studies), in favor of a fixed 300 mg dose of natalizumab in the two subsequent Phase 3 MS studies, Studies 1801 and 1802 (see Section 2.5.1, Fixed Dosing Regimen). A 300 mg fixed dose does not exceed 6 mg/kg in subjects weighing more than 50 kg, and is not less than 3 mg/kg in subjects weighing less than 100 kg. In Study 1801, the administration of 300 mg natalizumab IV resulted in mean  $\alpha$ 4-integrin saturation levels in excess of 90% immediately post-infusion and resulted in sustained (at Week 4 post-infusion)  $\alpha$ 4-integrin saturation levels of approximately 70%.

The sponsor has not initiated concurrently-controlled studies of greater than six months in duration using a natalizumab regimen other than 300 mg IV every 4 weeks. However, data from Study 231 provides evidence that natalizumab administration is associated with an elevation of serum leukocytes that persists for at least 8 weeks following natalizumab administration (see Figure 1). In addition, natalizumab administration every 4 weeks is associated with approximately 70% saturation of  $\alpha$ 4-integrin at trough (Week 4) natalizumab levels. Therefore, there is evidence suggesting that natalizumab may have sustained clinical activity with less frequent administration. The applicant has not investigated the safety and efficacy of less frequent administrations.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

The applicant proposes that natalizumab is indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations.

The sponsor has applied for accelerated approval of natalizumab for the above indication(s) based on results achieved after approximately one year of treatment in ongoing two-year clinical trials.

#### 6.1.1 Methods

Two large, multicenter, Phase 3, randomized, double-blind, placebo-controlled studies (1801 and 1802) provide the primary evidence of effectiveness for natalizumab in MS, and are the focus of this review. In the clinical development of natalizumab (see Section 4.2, Tables of Clinical Studies), these two Phase 3 studies were the only placebo-controlled studies that administered the proposed recommended dose of natalizumab to subjects with MS for more than six months.

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### 6.1.2 General Discussion of Endpoints

The clinical manifestations of MS include both relapses and progressive disability. The FDA has previously approved drugs for treatment of MS (see Section 2.2.1, Immune Modulators Approved for Treatment of MS) based on evidence of an effect on either the frequency of relapses (relapse rate) or progression of disability. These previous approvals have been based on data from two years of study agent administration in clinical trials. The clinical meaningfulness of an effect on relapse rate after only one year of study agent administration is unclear (see review memorandum of Dr. Marc Walton). The current application is for accelerated approval of natalizumab based on an effect on relapse rate using data from less than two years of study agent administration. The applicant proposes that the effect on relapse rate at one year, as presented in this application, can be used as a surrogate that is reasonably likely to predict an effect on relapse rate at two years (see Section 2.5.4, Application for Accelerated Approval).

Both the frequency and the occurrence of relapses can be clinically meaningful and can be useful as primary endpoints in Phase 3 MS trials. However, both of these outcome measures are subjective and susceptible to investigator bias. Therefore, blinding of assessors to treatment assignment is a critical element of the design of Phase 3 MS trials that use either of these outcomes as a primary or secondary endpoint. Pivotal trials of currently approved agents have often employed MRI outcomes as secondary endpoints (see Section 2, Introduction and Background). Although MRI assessments may also be subjective, blinding of MRI assessments can be extremely reliable; blinded assessors at a core laboratory can interpret the scans.

At the time of this review, Studies 1801 and 1802 are ongoing with a planned duration of slightly more than two years each. Each study specifies one co-primary endpoint at approximately one year based on the frequency of relapses on

This review does not assess the endpoints for the two-year analysis. All primary and secondary endpoints in Study 1801 are identical to the primary and secondary endpoints in 1802. This review of efficacy is based on analysis of the pre-specified one-year primary and secondary endpoints, which are described below.

To control the experiment-wise Type I error at 0.05 for the two co-primary endpoints, the protocol specified use of the Hochberg procedure (Hochberg, 1988). This procedure preserves the overall Type I error at 0.05. Applying the Hochberg procedure to the 1-year analysis, the p-value for the primary endpoint must be  $\leq 0.025$  to be considered statistically significant.

Analysis of the data from the first year was not an interim analysis in the conventional sense, in that a statistically positive result on the 1-year analysis would not result in early termination of the study.

Each Phase 3 protocol initially specified that the 1-year analysis would occur after subjects had undergone an average of 1 year of observation (projected as 900 subject-years for Study 1801 and 1200 patient-years for Study 1802). In order to more clearly specify the times of the 1-year



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analyses, each protocol was amended to prespecify cut-off dates for clinical and MRI outcome data to be included in the 1-year analyses.

- The 1801 protocol was amended to prespecify a clinical data cut-off date of July 17, 2003 and an MRI data cut-off date of August 12, 2003. The July 17, 2003 cut-off date included 988 total subject-years of observation into the 1-year analyses and occurred after all subjects remaining in the study completed at least the Week 48 visit.
- The 1802 protocol was amended to prespecify a clinical data cut-off date of October 15, 2003 and an MRI data cut-off date of October 31, 2003. The October 15, 2003 cut-off date included 1268 total subject-years of observation into the 1-year analyses and occurred after 98% of subjects remaining in the study completed at least the Week 24 visit.

Therefore, for each of the two Phase 3 Studies, the 1-year analyses described in this review are not based on one year of data for each subject, but rather are based on analyses that consider different lengths of study for the different subjects. This review describes these analyses and endpoints as "1-year" as a convenient approximation.

#### 6.1.2.1 Primary Endpoint for One-Year Analysis

The primary objective at 1 year was to determine whether natalizumab, when compared with placebo, was effective in reducing the rate of clinical relapses through 1 year. Annualized relapse rate was the protocol-specified primary endpoint, calculated using Poisson regression, adjusting for the number of relapses in the previous year, baseline EDSS, the presence of gadolinium enhancing lesions on T1-weighted MRI, and age. Subjects were censored at the time they added rescue treatment with an available alternative MS treatment, which was allowed per protocol once sustained progression was achieved.

The FDA assessed the use of the Poisson regression as statistically valid to classify each Phase 3 trial as either a success or failure based on the primary endpoint. However, CDER recognized that patients or physicians do not generally understand the Poisson regression. Therefore, CDER requested that the applicant provide additional analyses that calculate the mean annualized relapse rate for each study group based on individual relapse rates (number of relapses divided by number of years on study), and including all relapses that occurred during the study (i.e., including relapses that occurred following the initiation of an available alternative MS treatment). CDER efficacy analyses described in this review use this latter calculation of annualized relapse rate, without adjustment for age, baseline EDSS values, or baseline MRI findings.

#### 6.1.2.2 Secondary Endpoints for One-Year Analysis

The secondary endpoints at 1 year were the following:

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- 1) Reduction in the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, comparing the natalizumab group to the placebo group, using a pre-specified logit regression, adjusted for baseline number of T2 lesions (<9 versus ≥9 lesions). For this analysis, missing values were imputed using the mean number of T2-hyperintense lesions in the study population.
- 2) Reduction in the number of gadolinium-enhancing lesions on brain MRI scans, comparing the natalizumab group to the placebo group, using a pre-specified logit regression, adjusted for baseline number of gadolinium-enhancing lesions. For this analysis, missing values were imputed using the mean number of gadolinium-enhancing lesions in the study population.
- 3) Increase in the proportion of relapse-free subjects, comparing the natalizumab group to the placebo group, using a pre-specified logistic regression adjusted for the number of relapses in the one year prior to study entry. For this analysis, a subject was considered to have relapsed if either the subject withdrew from the study and did not experience a relapse prior to withdrawal, or the subject took alternative MS medications and did not experience a relapse.

The secondary endpoints were rank prioritized in the order presented above. If statistical significance ( $p < 0.05$ ) was not achieved for any secondary endpoint, all secondary endpoints(s) of a lower rank were not considered statistically significant.

Analysis of all MRI scans was performed at a central facility, either (Study 1801) or (Study 1802). Prior to subject enrollment at an investigational site, the MRI reading center verified the investigational site's scanning technique by evaluating a test scan from an MS subject. Original MRI tapes or optical disk media were sent by courier to the MRI center for review. Technicians and physicians at the central reading center evaluated the images for study-specific MRI endpoints. These physicians and technicians were blinded to the subjects' treatment assignments.

### 6.1.3 Study Design

The two Phase 3 trials, Studies 1801 and 1802, are very similar in design. Both are large, multicenter, international, randomized, double-blind, placebo-controlled, two-arm, two-year studies of natalizumab compared to placebo in subjects with relapsing MS. The designs of these two studies meet the regulatory requirements for adequate and well-controlled studies (21 CFR 314.126) to provide a reasonable assessment of the benefit of natalizumab in MS. The design of Study 1801 is described below, followed by a description of important differences between Studies 1801 and 1802.

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### 6.1.3.1 Design of Study 1801

#### 6.1.3.1.1 Study 1801 – Design

Study 1801 is a multicenter, international, randomized, double-blind, placebo-controlled, two-arm, parallel-group study in subjects with RRMS to assess the efficacy and safety of natalizumab. Approximately 900 subjects were to be randomized (2:1) at the baseline visit to receive either 300 mg of natalizumab or placebo by IV infusion every 4 weeks for up to 116 weeks. The co-primary endpoints are annualized relapse rate at 1 year and disability progression at 2 years.

Subjects were randomized at the Baseline Visit (Week 0) after all eligibility criteria (including a baseline EDSS score of 5.0 or lower) were confirmed. The randomization was stratified by site, using a centralized randomization schedule to balance the treatment group assignments within sites. The initial administration of study agent was to occur on the day of randomization (Week 0 visit).

A number of precautions were taken to preserve blinding throughout the study, including the following:

- 1) Centralized randomization stratified by site.
- 2) Study drug was administered in a blinded fashion such that neither the subject, the investigational site personnel, nor Biogen Idec knew a subject's treatment assignment. Only the \_\_\_\_\_ which was responsible for the randomization, was aware of the treatment assignment. The medical monitors at \_\_\_\_\_ were responsible for handling unblinding requests related to medical emergencies.
- 3) All study personnel at each study center were to be blinded to treatment assignment. Physicians, nurses, subjects, and any study personnel performing subject assessments were not to be informed of the subject's treatment assignment except in the event of a medical emergency or as required by regulatory authorities.
- 4) Investigational site personnel were not allowed to review laboratory leukocyte data, including the differential (with the exception of the absolute neutrophil count), which were obtained after the Screening Visit. White blood cell data, including the differential (with the exception of the absolute neutrophil count), which were obtained after the Screening Visit were not to be sent to the sites, but instead were to be reviewed centrally by an Independent Medical Monitor (IMM). Investigational sites were to be contacted periodically by the IMM for subject information to determine if the values were clinically significant.



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- 5) After Screening, MRIs were to be evaluated for non-MS pathology by physicians/technicians at the site who were blinded to the subjects' treatment assignments.
- 6) Each investigational site was to have four separate neurologists: a Treating Neurologist and a backup Treating Neurologist who oversaw subject management including the assessment and treatment of adverse events and new neurologic events and the review and sign-off of laboratory data, and an Examining Neurologist and a backup Examining Neurologist who conducted all EDSS evaluations at scheduled and, if necessary in the event of a relapse, at unscheduled visits. Analyses of all MRIs were performed by a central MRI reading center whose staff were blinded to treatment assignments.

The Examining Neurologist was not to be involved with any other aspect of subject care and management. The Examining Neurologist was not to serve as Treating Neurologist for any subjects at a study center. To ensure consistency across sites, Examining Neurologists were required to undergo a standardized training session on EDSS scoring prior to enrollment of subjects at their site. The backup Examining Neurologist was to conduct subject evaluations only if the primary Examining Neurologist was unavailable due to illness, vacation, or travel. All study centers were to attempt to maintain the same Examining Neurologist throughout the study. If an Examining Neurologist had to be replaced, the new Examining Neurologist was required to undergo a training session. The communication of new findings on the neurologic examination from the Examining Neurologist to the Treating Neurologist was permitted (because findings on the neurologic examination might be important in the routine care of the subject, e.g., medical management of relapses). The roles of Treating and Examining Neurologist (primary and backup) were not interchangeable even for different subjects. However, the Examining Neurologist could also act as the Examining Technician. The Examining Neurologist was to remain blinded to adverse events, concomitant medications, laboratory data, MRI data, and any other data that had the potential of revealing subject treatment assignments.

- 7) Absolute neutrophil count data were sent to the investigational sites to aid in management of the subject, but, as with other laboratory and clinical information, was not to be reviewed by the Examining Neurologist, the backup Examining Neurologist, the Examining Technician, or the backup Examining Technician.
- 8) Either the Examining Technician or the Examining Neurologist administered the components of the Multiple Sclerosis Functional Composite (MSFC) at screening, baseline, and throughout the study.

Of note, the use of separate treating and examining neurologists has become a critical element to provide for blinded assessment of clinical outcome measures for many MS clinical trials. For trials of interferon betas, this approach was essential because of adverse events that would likely lead to unblinding of the treating neurologist. For Studies 1801 and 1802, this same approach

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was used, although there was no clear evidence from the Phase 1 and Phase 2 studies that natalizumab would cause adverse events that were likely to be unblinding. The major exception was the known pharmacodynamic effect of natalizumab on peripheral leukocyte counts, but the methods employed above to blind the study personnel to laboratory data should have been sufficient. Overall, the methods to preserve blinding were adequate.

All study management, investigational site personnel, investigators, and subjects directly involved in the study were to remain blinded to subject treatment assignment until the conclusion of the 2-year study, except if a subject experienced a medical emergency that necessitated unblinding the subject's treatment assignment.

Prohibited concomitant medications included any investigational product, including investigational symptomatic treatment for MS, any "alternative drug treatments directed towards the treatment of MS such as chronic immunosuppression," and any steroid therapy, except for protocol-defined treatment of relapse. Permitted concomitant medications included symptomatic treatments (e.g., treatments for spasticity, depression, or fatigue). The decision on whether or not to treat a relapse was at the discretion of the Treating Neurologist. The protocol-specified treatment for relapses was methylprednisolone 1000 mg IV QD or in divided doses, for either 3 days or 5 days, with the duration of treatment at the discretion of the Treating Neurologist. Subjects were not to begin corticosteroid treatment of a possible relapse until they had been examined by the Examining Neurologist. Retreatment of the same relapse was not allowed unless approved by the Advisory Committee.

Subjects who experienced significant disease progression as defined by the protocol (at least a 1.0 point increase on the EDSS from a baseline EDSS  $\geq 1.0$  that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks) were to be notified that they had experienced worsening of physical disability. These subjects were to be given the option to continue study drug and all follow-up visits per protocol or to add treatment with either IFN- $\beta$  or glatiramer acetate. The subject was to document this decision by signing an addendum to the Informed Consent Form. All safety monitoring, study visits, clinical evaluations, and MRI evaluations were to continue as planned.

An Advisory Committee was formed to provide scientific and medical direction and to oversee the administrative progress of the study. The Advisory Committee was to meet at least monthly to monitor subject accrual and noncompliance with the protocol at individual investigational sites. The Advisory Committee determined whether the study should be stopped or amended for reasons other than safety.

A Safety Monitoring Committee (SMC) was formed to review the safety data and to advise the sponsor with regard to study discontinuation for safety reasons. The operating guidelines for the SMC were pre-specified and included scheduled meetings approximately 1 year and 2 years after enrollment began on Study 1801. Every month, the Study Director was to forward to the members of the SMC copies of enrollment numbers and incidence and available details on serious adverse events (SAEs). Details of SAEs that were unexpected and associated with the use of the drug were to be forwarded to SMC members as information became available. Any

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information that was unblinded to treatment assignment was to be treated as confidential. Membership of the SMC consisted of independent medical and statistical personnel who were not allowed to participate as investigators in any natalizumab study sponsored by Elan Pharmaceuticals, Inc. or Biogen Idec.

#### 6.1.3.1.2 Study 1801 – Study Agent Administration

Infusions of 300 mg natalizumab or placebo were to be administered every 4 weeks for up to 116 weeks.

The study agent was provided in 5 mL vials stored at 2 – 8°C. Study agent from 3 vials (a total of 15 mL) was injected into a 100 mL bag of 0.9% saline. The study agent in solution was then allowed to warm to room temperature prior to administration. The diluted study agent was administered by IV infusion over approximately 60 minutes. Study agent administration was to begin within 5 hours following study agent dilution in normal saline.

The study agent was administered in a clinical setting under the supervision of a physician. Each subject was monitored in the clinic for at least one hour following the completion of study agent infusion.

#### 6.1.3.1.3 Study 1801 – Eligibility Criteria

##### 6.1.3.1.3.1 Study 1801 – Inclusion Criteria

All subjects were required to meet all of the following criteria:

- 1) Male and female subjects between 18 and 50 years of age, inclusive
- 2) had a diagnosis of MS as defined by McDonald et al, criteria 1-4 (see Appendix 10.3, McDonald Diagnostic Criteria for MS)
- 3) had a baseline EDSS score between 0.0 and 5.0, inclusive (see Appendix 10.4, Kurtzke Expanded Disability Status Scale)
- 4) had a brain MRI scan demonstrating lesion(s) consistent with MS
- 5) had at least 1 medically documented clinical relapse within the 12 months prior to randomization. For the purpose of this inclusion criterion, a relapse was defined as neurologic signs and/or symptoms documented in the medical record and of sufficient duration to be determined by the investigator or the treating physician as consistent with an MS relapse. The January 11, 2002 protocol amendment clarified that the 12-month interval between the relapse and randomization was to start at the time of relapse onset.

##### 6.1.3.1.3.2 Study 1801 – Exclusion Criteria

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Patients were excluded from enrollment if any of the following exclusion criteria existed at the time of randomization:

- 1) Primary progressive, secondary progressive, or progressive-relapsing MS, as defined by Lublin and Reingold, 1996. These conditions require the presence of continuous clinical disease worsening over a period of at least 3 months. Subjects with these conditions may also have superimposed relapses, but are distinguished from relapsing-remitting subjects by the lack of clinically stable periods or clinical improvement. This definition of progressive MS was added by the January 11, 2002 protocol amendment.
- 2) MS relapse occurred, in the opinion of the investigator, within 50 days prior to randomization and/or the subject had not stabilized from a previous relapse, in the opinion of the investigator, prior to randomization.
- 3) A clinically significant infectious illness within 30 days prior to randomization.
- 4) History of, or abnormal laboratory results indicative of, any significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, and/or other major disease, which, in the opinion of the investigator, would preclude the administration of a recombinant humanized antibody immunomodulating agent for 116 weeks.
- 5) History of severe allergic or anaphylactic reactions or known drug hypersensitivity.
- 6) Unable to perform the Timed 25-Foot Walk, 9 Hole Peg Test (HPT) (with both upper extremities), and Paced Auditory Serial Addition Test (PASAT 3).
- 7) Abnormal blood tests, performed at the screening visit, which exceeded any of the limits defined below:
  - Alanine transaminase/serum glutamate-pyruvate transaminase (ALT/SGPT), or aspartate transaminase/serum glutamic-oxaloacetic transaminase (AST/SGOT) >3 times the upper limit of normal (ULN).
  - Total WBC count < 2,300/mm<sup>3</sup>.
  - Platelet count <100,000/mm<sup>3</sup>.
  - Creatinine >2 times the ULN.
  - Prothrombin time (PT) > ULN.

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- 8) Treatment with cyclosporine, azathioprine, methotrexate, subcutaneous glatiramer acetate, interferon beta, intravenous immunoglobulin, plasmapheresis, or cytappheresis within 6 months prior to randomization.
- 9) History of treatment with either an interferon  $\beta$  for a total of at least 6 months, or glatiramer acetate for a total of at least 6 months.
- 10) Any prior treatment with total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, natalizumab, or any other therapeutic monoclonal antibody.
- 11) Treatment with mitoxantrone or cyclophosphamide within 1 year prior to randomization.
- 12) Treatment with oral glatiramer acetate within 3 months prior to Screening (added by the January 11, 2002 protocol amendment).
- 13) Treatment with IV corticosteroids, oral corticosteroids, 4-aminopyridine, or products related to 4-aminopyridine, within 50 days prior to randomization. 4-aminopyridine was added by the January 11, 2002 protocol amendment. Products related to 4-aminopyridine were added by the September 15, 2003 protocol amendment.
- 14) History of alcohol or drug abuse within 2 years prior to randomization.
- 15) Female subjects who were not postmenopausal for at least 1 year, surgically sterile, or who were not willing to practice effective contraception (as defined by the investigator) during the study. The rhythm method was not to be used as the sole method of contraception.
- 16) Nursing mothers, pregnant women, and women who planned to become pregnant while on study.
- 17) Participation in previous natalizumab studies (unless subject was on placebo). A clarification that placebo subjects who experienced adverse events during those studies may also be excluded was added by the January 11, 2002 protocol amendment.
- 18) Participation in any other investigational study within 6 months prior to randomization.

#### 6.1.3.1.4 Study 1801 – Study Procedures

Screening studies, to be performed within 35 days prior to randomization, included baseline laboratory studies (urinalysis, hematology, chemistry profile), pregnancy test for women of childbearing potential, physical examination, EDSS examination, brain MRI with and without gadolinium, Multiple Sclerosis Functional Composite (MSFC; repeated 3 times within 35 days prior to randomization), and optional genetic testing.

The scheduling of all visits was calculated based on the baseline visit date. The protocol specified several types of clinic visits:

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- 1) Study Drug Administration Visits (SDAVs) occurred at baseline and every 4 weeks (+/- 3 days) through Week 116. These visits included monitoring of adverse events and concomitant medications, a urine pregnancy test for women of childbearing potential, and study agent administration.
  - 2) Clinical Evaluation Visits (CEVs) of two types:
    - a. Scheduled – at baseline and every 12 weeks (+/- 1 week) through Week 120; each Scheduled CEV included a physical examination, laboratory studies (urinalysis, hematology, and chemistry panel), anti-natalizumab antibody sample, and MSFC and EDSS examinations.
    - b. Unscheduled – Subjects were to telephone the Treating Neurologist within 48 hours of the onset of any new neurologic symptom that might indicate a relapse. An Unscheduled Visit was to be scheduled for within 72 hours of the suspected relapse. The Treating Neurologist determined whether a relapse may have occurred, and, if so, referred the subject to the Examining Neurologist. The Examining Neurologist performed an EDSS examination within 5 days of the suspected relapse.
- A selected cohort of subjects also had PK/PD tests to measure natalizumab levels and  $\alpha$ 4-integrin saturation of mononuclear cells, monthly for 3 months and then every 3 months to the end of the study. Limited PK and PD measures (WBCs and lymphocytes) were to be assessed in all subjects.
- 3) MRI Evaluation Visits (MEVs) occurred at baseline and Weeks 52 and 104 (+/- 4 weeks). The brain MRI scan was not to be performed during the 5 days following the administration of study drug or within 30 days of receiving a course of steroids.
  - 4) An End of Study Visit was scheduled for Week 128, including physical examination, a urine pregnancy test for women of childbearing potential, laboratory (urinalysis, hematology, and chemistry panel), PK/PD sample for a selected cohort of subjects, anti-natalizumab antibody sample, and MSFC and EDSS examinations. These same procedures were applied for a premature study termination visit.

#### 6.1.3.1.5 Study 1801 – Endpoints and Analysis Plan

The primary endpoint for the 1-year analysis, which serves as the basis for this application, was the effect of natalizumab compared to placebo on the annualized relapse rate. For this study, a relapse was defined as new or recurrent neurologic symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurological findings. This determination of whether an event was associated with new objective neurological findings was based on the assessment by the Examining Neurologist. In order to be counted as a relapse, the onset of a relapse was required to be at least 30 days following the onset of the previous relapse. If the onset of a relapse was less than 30 days following the onset of the previous



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relapse, the relapse was considered an extension of the previous relapse and was not counted as an additional event.

See Section 6.1.2, General Discussion of Endpoints for a discussion of the co-primary endpoints (Section 6.1.2.1, Primary Endpoint for 1-year Analysis) and secondary endpoints (Section 6.1.2.2, Secondary Endpoints for 1-year Analysis).

#### 6.1.3.2 Design of Study 1802

The design of Study 1802 was very similar to the design of Study 1801. Major features of Study 1802 that were different from the design of Study 1801 were the following:

- 1) Target enrollment of approximately 1200 subjects;
- 2) 1:1 randomization to either natalizumab or placebo;
- 3) Inclusion criterion – subjects between 18 and 55 years of age, inclusive;
- 4) Inclusion criterion that all subjects must have received Avonex<sup>®</sup> for at least 12 months prior to randomization;
- 5) Exclusion criterion that subjects must not have received any interferon product other than Avonex<sup>®</sup> within 1 year prior to randomization;
- 6) Subjects were to receive 30 µg Avonex<sup>®</sup> by IM injection once a week, administered by either the subjects or their designees, throughout the study. Avonex<sup>®</sup> was not to be administered within 24 hours of the IV infusion of study drug.

#### 6.1.4 Efficacy Findings

This efficacy review is based primarily on two Phase 3 studies, Studies 1801 and 1802 (see Section 4, Data Sources, Review Strategy, and Data Integrity and Section 6.1.3, Study Design). Study 1801 compares natalizumab to placebo; Study 1802 compares natalizumab to placebo as an add-on therapy to Avonex<sup>®</sup>. Both studies enrolled subjects with active RRMS, with activity defined by the occurrence of at least one relapse during the year prior to randomization. In Study 1801, 11% of subjects were enrolled at U.S. sites, whereas 62% of subjects in Study 1802 were enrolled at U.S. sites.

##### 6.1.4.1 Subject Enrollment, Study 1801

Study 1801 included 99 investigators in North America, Europe, Australia, and New Zealand who enrolled and randomized a total of 942 subjects. Seventy investigators in Europe enrolled 697 subjects, 24 investigators in North America enrolled 213 subjects, and 5 investigators in Australia and New Zealand enrolled 32 subjects. Forty-one sites enrolled at least 10 subjects and



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collectively accounted for 624 subjects, or 66% of the total population; 19 sites enrolled fewer than 5 subjects.

Of the 942 subjects enrolled in the study, 315 were randomized to receive placebo and 627 were randomized to receive natalizumab.

The first subject received the first dose on November 6, 2001. The cut-off date for the analysis was July 15, 2003; however data from subject 109-009 were included even though the subject's Week 52 visit occurred on July 17, 2003. In order to capture MRI data for the majority of subjects, MRI evaluations performed through August 12, 2003 were included in the database.

#### 6.1.4.2 Subject Enrollment, Study 1802

Study 1802 enrolled and randomized a total of 1196 subjects. However, Site # which enrolled 25 subjects, was closed by the sponsor due to protocol noncompliance. The data from Site were excluded from the applicant's efficacy analyses. The remaining 123 sites in North America, Europe, and Israel enrolled a total of 1171 subjects.

Seventy investigators in North America enrolled 724 subjects, 51 investigators in Europe enrolled 417 subjects, and 2 investigators in Israel enrolled 30 subjects. Fifty-five sites enrolled at least 10 subjects and collectively accounted for 815 subjects, or 70% of the total population; 30 sites enrolled fewer than 5 subjects.

Of the 1171 remaining subjects enrolled in the study, 582 were randomized to receive placebo plus Avonex<sup>®</sup>, and 589 were randomized to receive natalizumab plus Avonex<sup>®</sup>.

The first subject received the first dose on January 14, 2002. The cut-off date for data to be included in the one-year analyses was October 15, 2003; however, in order to include MRI data from the majority of subjects, MRI data from evaluations performed through October 31, 2003, were included in the one-year analyses.

**Because Studies 1801 and 1802 were similar in design, the results of the two studies are presented together in this review.**

#### 6.1.4.3 Baseline Characteristics

Treatment groups in both studies were well-matched with regard to demographics and baseline disease characteristics (Table 3). The study subjects were predominantly female, consistent with the U.S. MS population at large. The study subjects were almost entirely Caucasian, with an under-representation of minorities relative to the U.S. MS population.

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<b>Table 3: Baseline Characteristics</b>				
	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex <sup>®</sup>	Natalizumab + Avonex <sup>®</sup>
N	315	627	582	589
Age (mean $\pm$ SD, years)	36.7 $\pm$ 7.8	35.6 $\pm$ 8.5	39.1 $\pm$ 7.6	38.8 $\pm$ 7.7
Age (median, years)	37	36	39	39
Age, 25 <sup>th</sup> , 75 <sup>th</sup> percentile, years	31, 43	29, 43	34, 45	33, 44
Female – N, (%)	211 (67)	449 (72)	420 (72)	442 (75)
Caucasian – N, (%)	296 (94)	602 (96)	542 (93)	551 (94)
African Ancestry – N, (%)	6 (2)	5 (<1)	22 (4)	17 (3)
Hispanic – N, (%)	6 (2)	8 (1)	9 (2)	12 (2)
Weight (mean $\pm$ SD, kilograms)	72.2 $\pm$ 16.0	71.8 $\pm$ 16.1	73.0 $\pm$ 16.9	72.5 $\pm$ 17.1
Weight (median, kilograms)	70.7	69.0	70.0	70.0
Weight, 25 <sup>th</sup> , 75 <sup>th</sup> percentile, kilograms	60.0, 81.0	60.0, 80.0	60.0, 83.0	60.0, 82.0
McDonald 1 – number of subjects (%)	261 (83)	528 (84)	532 (91)	538 (91)
Years since MS onset (median) (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	5.9 (2.0, 11.0)	5.0 (2.7, 10.0)	8.0 (4.3, 13.8)	7.2 (4.1, 12.4)
Relapses – previous 3 years (median) (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	2 (2, 3)	3 (2, 3)	3 (2, 4)	3 (2, 4)
Relapses – previous 1 year (median) (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Relapses – previous year = 0 (n, %)	6 (1.9)	6 (1.0)	1 (0.2)	0 (0.0)
Relapses – previous year = 1 (n, %)	180 (57.1)	368 (58.7)	365 (61.3)	398 (66.4)
Relapses – previous year = 2 (n, %)	102 (32.4)	197 (31.4)	179 (30.1)	157 (26.2)
Relapses – previous year = 3 (n, %)	20 (6.3)	43 (6.9)	39 (6.6)	32 (5.3)
Relapses – previous year = 4 (n, %)	5 (1.6)	9 (1.4)	10 (1.7)	8 (1.3)
Relapses – previous year $\geq$ 5 (n, %)	2 (0.6)	4 (0.6)	1 (0.2)	4 (0.7)
Months since most recent relapse (median) (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	5.7 (3.8, 8.8)	5.6 (3.7, 8.3)	5.1 (3.3, 7.8)	5.1 (3.4, 7.6)
EDSS (median) (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	2 (1.5, 3.0)	2 (1.5, 3.0)	2.5 (1.5, 3.5)	2 (1.5, 3.0)
Gadolinium-enhancing lesions (median) (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	0 (0, 2)	1 (0, 2)	0 (0, 1)	0 (0, 1)
T2 lesions $\geq$ 9 – number of subjects (%)	298 (95)	595 (95)	528 (91)	920 (88)

Relative to the subjects in Study 1801, subjects in Study 1802 were slightly older, with a longer duration of MS, on average. This is consistent with the fact that subjects in 1802 had been maintained previously on Avonex<sup>®</sup>, whereas the majority of subjects in 1801 had never received a beta-interferon.

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#### 6.1.4.4 Study Conduct

The overall conduct of Studies 1801 and 1802 is outlined in Table 4. At the time of the one-year analyses, less than 15% of subjects enrolled in each study had discontinued study agent, and less than 8% of the subjects enrolled in each study had withdrawn. Subjects who discontinued study drug or withdrew from the study due to an adverse event are described further in the Safety Review, Section 7.1.3, Dropouts and Other Significant Adverse Events.

<b>Table 4: Disposition of Subjects</b>				
	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex®	Natalizumab + Avonex®
Randomized - N	315	627	582	589
Withdrew prior to dosing - N, (%)	3 (1)	0	0	0
Dosed - N, (%)	312 (99)	627 (100)	582 (100)	589 (100)
Completed 1 year in study - N, (%)	280 (89)	568 (91)	387 (66)	393 (67)
≥ 13 infusions - N (%)	285 (90)	583 (93)	451 (78)	456 (77)
Discontinued study drug - N, (%)	25 (8)	44 (7)	70 (12)	61 (10)
Discontinued due to adverse event - N, (%)	8 (3)	31 (5)	24 (4)	16 (3)
Deaths - N, (%)	0	0	1 (<1)	0
Withdrew from study - N, (%)	18 (6)	21 (3)	41 (7)	29 (5)
Withdrew due to adverse event - N, (%)	6 (2)	12 (2)	4 (<1)	7 (<1)
Took an alternative MS drug - N (%)	21 (7)	19 (3)	19 (3)	6 (1)

Three subjects randomized to receive placebo in Study 1801 withdrew from the study prior to receiving study treatment; all other subjects received at least 1 dose of study agent.

Protocol violations are summarized in Table 5. In each study, the frequency of protocol violations of each type is similar for the two treatment arms, adjusted for the number of subjects in each arm. These violations were minor, and would not be expected to affect the results directionally.

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**Table 5: Protocol Violations**

	Study 1801				Study 1802			
	Natalizumab N = 627		Placebo N = 315		Natalizumab N = 589		Placebo N = 582	
Type of Violation	number of violations	number of subjects (%)	number of violations	number of subjects (%)	number of violations	number of subjects (%)	number of violations	number of subjects (%)
Eligibility criteria violation	64	52 (8.3%)	33	27 (8.6%)	88	70 (11.9%)	88	67 (11.5%)
Missed, partial, or incorrect dosing	323	144 (23%)	145	77 (24.4%)	868	306 (52%)	918	310 (53.3%)
Prohibited concomitant medication	29	22 (3.5%)	17	11 (3.5%)	69	55 (9.3%)	72	53 (9.1%)
Outside acceptable visit window	1239	406 (64.8%)	692	218 (69.2%)	1423	418 (71%)	1504	430 (73.9%)
Efficacy evaluation not performed or not valid	104	73 (11.6%)	60	45 (14.3%)	189	113 (19.2%)	197	107 (18.4%)
Safety evaluation not performed or not valid	162	103 (16.4%)	95	53 (16.8%)	185	101 (17.1%)	213	120 (20.6%)
Missed study visit	38	25 (4%)	22	13 (4.1%)	39	29 (4.9%)	54	39 (6.7%)
Other	994	399 (63.6%)	529	208 (66%)	1633	407 (69.1%)	1790	418 (71.8%)
Not classified*	2	2 (0.3%)	0	0 (0%)	6	4 (0.7%)	9	7 (1.2%)
Total	2955	554 (88.4%)	1593	291 (92.4%)	4500	569 (96.6%)	4855	568 (97.6%)

\* Events that were not classified were reviewed individually by CDER and were all deemed minor violations.

#### 6.1.4.5 Efficacy Results – Primary Endpoint

##### 6.1.4.5.1 Applicant's Analyses

For the 1-year analysis in Study 1801, annualized relapse rates were 0.261 (95% CI: 0.211, 0.323) and 0.805 (95% CI: 0.669, 0.969) in the natalizumab and placebo groups, respectively

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( $p < 0.001$ ). In Study 1802, the respective annualized relapse rates were 0.383 (95% CI: 0.325, 0.450) vs. 0.816 (95% CI: 0.721, 0.923) in the natalizumab plus Avonex<sup>®</sup> versus the placebo plus Avonex<sup>®</sup> groups ( $p < 0.001$ ). The applicant's analyses use a Poisson regression to calculate the annualized relapse rate and consider relapses and time on study up to the time of initiation of an alternative MS drug. Relapse rates were adjusted for the number of relapses in the one year prior to study entry, baseline EDSS, presence of gadolinium-enhancing lesions on MRI, and age. The applicant's analysis results were confirmed by CDER.

Both 1801 and 1802 employed randomization stratified by center. However, the applicant assessed that inclusion of study center in the analysis model was not feasible due to the relatively large number of small centers. After extensive internal discussion, CDER informed the sponsor during a telephone call on October 28, 2003, that the primary analysis model need not include a term for the study center.

#### 6.1.4.5.2 CDER Analyses

CDER performed exploratory analyses and calculated annualized relapse rates as the mean of the individual relapse rates for all subjects in a group. Relapse rates for individual subjects were calculated as the number of relapses divided by the number of days on study, multiplied by 365.25 days/year. Thus, all subjects contributed equally to the calculation of annualized relapse rate, irrespective of their time on study. CDER's calculations include all confirmed relapses, specifically including relapses on study after initiation of an alternative MS treatment. The results of CDER's analyses of the annualized relapse rates (Table 6), using a t-test, are very similar to the results from the applicant's analyses, using Poisson regression. For all CDER analyses, relapse rates are reported with units of person<sup>-1</sup>·years<sup>-1</sup>.

<b>Table 6: CDER Analysis of Annualized Relapse Rate, All Subjects</b>				
	Study 1801		Study 1802	
	Placebo N = 315	Natalizumab N = 627	Placebo + Avonex <sup>®</sup> N = 582	Natalizumab + Avonex <sup>®</sup> N = 589
Mean	0.735	0.250	0.780	0.357
Standard Deviation	1.126	0.533	1.002	0.620
Median	0	0	0.685	0
Range	0-6.408	0-3.454	0-6.764	0-3.414

#### 6.1.4.5.2.1 Exploration of Irregularities

Site # With respect to the protocol non-compliance at Site #. (Study 1802), CDER conducted sensitivity analyses to assess the extent to which the exclusion of these data might affect the study results. CDER conducted a "worst case" analysis of the primary endpoint, imputing a relapse rate of 0 for each of the 13 placebo group subjects, and a relapse rate of 1 for each of the 12 natalizumab group subjects. Using this imputation scheme, treatment with natalizumab was associated with a 52% relative decrease in annualized relapse rate (0.763 vs.

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0.370) compared to placebo. Clearly, therefore, the sponsor's decision to exclude data from Site — would not importantly affect the overall study results, and CDER excluded these data as well.

Subject #146-105 (Study 1802): This subject (in the placebo group) was initially reported by the applicant to have had a first relapse on \_\_\_\_\_ and a second relapse on \_\_\_\_\_ and the sponsor included both relapses in the primary analysis. However, after a review of the available data, the sponsor assessed the \_\_\_\_\_ "relapse" as a continuation of the \_\_\_\_\_ relapse. Only the \_\_\_\_\_ relapse and not the \_\_\_\_\_ relapse" is included in CDER analyses. This results in a minor discrepancy between the results of the applicant's analyses and CDER analyses.

Use of alternative MS treatment: As noted above, CDER included all time on study for these subjects, irrespective of the initiation of treatment with alternative MS treatment.

#### 6.1.4.5.2.2 Financial conflicts of interest

CDER conducted analyses of the primary endpoint excluding data from all sites with reported financial conflicts of interest. This included 6 sites in Study 1801 that enrolled 16 subjects into the placebo group and 30 subjects into the natalizumab group, as well as 12 sites in Study 1802 that enrolled 76 subjects into the placebo + Avonex<sup>®</sup> group and 79 subjects into the natalizumab + Avonex<sup>®</sup> group. In the sites with no reported financial conflicts of interest, treatment with natalizumab resulted in a 67% decrease in annualized relapse rate (0.735 vs. 0.246) compared to placebo (Study 1801). Treatment with natalizumab + Avonex<sup>®</sup> resulted in a 55% decrease in annualized relapse rate (0.756 vs. 0.340) compared to placebo + Avonex<sup>®</sup> in Study 1802. Thus, if there were investigator biases at these sites, due to financial or other conflicts of interest, as well as unblinding, they would not have importantly affected the overall study results.

#### 6.1.4.5.2.3 Relapses by Severity

Natalizumab appears to decrease the rate of severe relapses and relapses treated with steroids, proportionate to the overall decrease in relapse rate (Table 7; Table 8). Natalizumab administration in Study 1802 is also associated with a proportionate decrease in the number of serious relapses. However, the number of serious relapses is very low, so the strength of this observation is limited.

**Table 7: Mean Annualized Relapse Rate, by Severity, Study 1801\***

Study 1801	Number of relapses		Relapse rates (mean annualized)		
	Placebo N = 315	Natalizumab N = 627	Placebo N = 315	Natalizumab N = 627	% change
All relapses	235 (100)	165 (100)	0.735	0.250	66% decrease
Serious relapses*	4 (2%)	9 (5%)	0.012	0.013	8% increase
Severe relapses*	15 (6%)	10 (6%)	0.047	0.014	70% decrease
Relapses treated with steroids*	168 (71%)	105 (64%)	0.542	0.158	71% decrease



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\* Percentages represent percent of all relapses.

Only 2 relapses, one in each 1801 study group, resulted in discontinuation of study agent.

<b>Table 8: Mean Annualized Relapse Rate, by Severity, Study 1802<sup>1</sup></b>					
Study 1802	Number of relapses		Relapse rates (mean annualized)		
	Placebo N = 582	Natalizumab N = 589	Placebo N = 582	Natalizumab N = 589	% change
All relapses <sup>2</sup>	478 (100)	225 (100)	0.780	0.357	54% decrease
Serious relapses <sup>2</sup>	7 (1%)	1 (0.4%)	0.011	0.001	91% decrease
Severe relapses <sup>2</sup>	34 (7%)	19 (8%)	0.057	0.030	47% decrease
Relapses treated with steroids <sup>2</sup>	397 (83%)	156 (69%)	0.645	0.243	62% decrease

<sup>1</sup> Excludes site 473 data

<sup>2</sup> Percentages represent percent of all relapses.

Ten relapses, 9 in the placebo + Avonex<sup>®</sup> group and 1 in the natalizumab + Avonex<sup>®</sup> group, resulted in discontinuation of study agent.

The slightly higher rate of steroid use in the placebo groups, compared to the natalizumab groups, is difficult to interpret, but may suggest that relapses were more severe in the placebo group. The higher use of steroids in the placebo group could also reflect investigator bias, if the Treating Neurologist were able to ascertain or guess a subject's treatment assignment and expected that subjects receiving placebo were more likely to need steroids. If steroids have any effect on the incidence of a subsequent relapse, the higher rate of steroid use in the placebo group might bias the overall study results. However, such a bias would favor the placebo group, leading to an underestimate of the benefit of natalizumab.

<b>Table 9: Distribution of Relapse Severity, Studies 1801 and 1802</b>				
Relapses	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex <sup>®</sup>	Natalizumab + Avonex <sup>®</sup>
Total number*	235 (100%)	165 (100%)	478 (100%)	225 (100%)
Severe relapses*	15 (6%)	10 (6%)	34 (7%)	19 (8%)
Moderate relapses*	112 (48%)	77 (47%)	309 (65%)	133 (59%)
Mild relapses*	108 (46%)	78 (47%)	135 (28%)	73 (32%)

\* Percentages represent percent of all relapses.

The distributions of relapse severities (Table 9) were strikingly similar between the natalizumab and control groups; this was true in both studies. Thus, the decrease in relapse rate associated with natalizumab is not accompanied by a shift to milder or more severe relapses. Additional analyses examined the frequency of relapses requiring steroids and the proportion of subjects



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who had severe relapses in each of the two Phase 3 studies; these analyses are presented in Table 10. The numbers of subjects with serious relapses were too small for meaningful analysis.

Table 10: Numbers of Subjects with Severe Relapses and Relapses Requiring Steroids					
	Placebo	Natalizumab	Relative risk <sup>1</sup> (95% CI)	Decreased risk of relapse associated with natalizumab	
				Absolute	Relative
Severe relapses					
Study 1801	12 / 315 (3.8%)	9 / 627 (1.4%)	0.38 (0.16, 0.88)	2.4%	62%
Study 1802	30 / 582 (5%)	17 / 589 (3%)	0.56 (0.31, 1.00)	2.3%	44%
Relapses requiring steroids					
Study 1801	105 / 315 (33%)	88 / 627 (14%)	0.42 (0.33, 0.54)	19%	58%
Study 1802	256 / 582 (44%)	129 / 589 (22%)	0.50 (0.42, 0.59)	22%	50%

<sup>1</sup> Relative risk of being severe relapse-free or steroid-treated relapse-free, comparing natalizumab group to placebo group. Subjects with no relapses prior to alternative MS drug or prior to dropping out of the study were all considered to have no relapses.

Note the analyses presented in Table 10 support the consistency of natalizumab's effect.

#### 6.1.4.5.3 Primary Endpoint, Subgroup Analyses

Results of subgroup analyses are shown in (Table 11).

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**Table 11: Primary Efficacy Endpoint, Annualized Relapse Rate - Subgroup Analysis**

	Study 1801					Study 1802				
	Natalizumab		Placebo		reduction (%)	Natalizumab		Placebo		reduction (%)
	n	relapse rate	n	relapse rate		n	relapse rate	n	relapse rate	
<b>Overall</b>	627	0.25	315	0.735	66.0%	245	0.253	265	0.687	63.2%
<b>Gender</b>										
male	178	0.247	104	0.713	65.4%	147	0.326	162	0.789	58.7%
female	449	0.251	211	0.746	66.4%	442	0.367	420	0.776	52.7%
<b>Race</b>										
Caucasian	602	0.25	296	0.724	65.5%	551	0.355	542	0.759	53.2%
African descent	5	0.187	6	0.776	75.9%	17	0.451	22	0.712	36.7%
Asian	3	0	3	1.72	100.0%	2	2.182	4	1.251	-74.4%
Hispanic	8	0.303	6	0.911	66.7%	12	0.121	9	1.332	90.9%
<b>Age</b>										
≤ 37 yrs (median)	345	0.239	165	0.911	73.8%					
> 37 yrs (median)	282	0.262	150	0.543	51.7%					
≤ 39 yrs (median)						303	0.357	295	0.917	61.1%
> 39 yrs (median)						286	0.357	287	0.639	44.1%
<b>Weight (kilograms)</b>										
< 50	16	0.183	14	0.776	76.4%	20	0.482	16	1.293	62.7%
50 - 59.9	134	0.289	55	1.176	75.4%	124	0.349	117	0.813	57.1%
60 - 69.9	172	0.216	83	0.74	70.8%	143	0.424	149	0.716	40.8%
70 - 79.9	140	0.26	68	0.632	58.9%	122	0.276	123	0.759	63.6%
80 - 89.9	76	0.239	51	0.486	50.8%	90	0.304	79	0.878	65.4%
90 - 99.9	46	0.33	29	0.75	56.0%	40	0.451	48	0.596	24.3%
100 - 109.9	20	0.273	7	0.373	26.8%	24	0.293	26	0.628	53.3%
110 - 150	22	0.116	7	0.369	68.6%	20	0.522	19	0.96	45.6%
<b>Region</b>										
United States	71	0.24	37	0.555	56.8%	363	0.312	361	0.729	57.2%
Not USA	556	0.251	278	0.759	66.9%	226	0.429	221	0.862	50.2%

The treatment effect of natalizumab is generally robust across all subgroups. It is consistent in both genders. Numbers of minority subjects were too small to reliably assess differences; however, the effect trended in favor of natalizumab in subjects of African and Hispanic descent. There were only 6 Asian subjects in each study, a number too small to interpret the apparent diametrically opposed outcomes in the two studies. Of note, race information is missing or classified as "Other" for 13 subjects in 1801, 12 subjects in 1802.

In general, MS relapse rates were lower for older subjects. This tendency may be related to changes in immune response with aging, and there is the possibility that older MS subjects may be less likely to derive benefit from immune-modifying therapies. The tendency for older subjects to have lower relapse rates is seen in data from the placebo groups in both studies. In natalizumab groups of both studies, however, annualized relapse rates were virtually the same in younger and older subjects. Thus, natalizumab treatment was associated with a greater treatment

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effect in younger subjects in both studies. Nevertheless, the treatment effect appears to be fairly impressive, even in older subjects (52% and 44% relative reductions in annualized relapse rates in Studies 1801 and 1802, respectively).

Data from Study 1801 tends to show a slightly greater treatment effect in individuals of lower weight; however, there was a trend in the opposite direction in Study 1802 (see Section 2.5.1, Fixed Dosing Regimen). Specifically, in Study 1801, there was a 73% reduction in annualized relapse rate in natalizumab-treated subjects weighing under 70 kg (70 kg was close to median weight in both studies), and a 56% reduction in annualized relapse rate in natalizumab-treated subjects weighing  $\geq 70$ kg. In Study 1802, the corresponding percent reductions were 50% and 57%. Thus, the trends in Studies 1801 and 1802 were directionally opposite, and there is no clear signal to suggest that subjects of greater weight were inadequately dosed.

The activity of natalizumab is generally consistent within and outside the U.S.

Table 12 shows the annualized relapse rates for disease-related subgroups. There is no consistent relationship between baseline disability, as measured on the EDSS, and the percent reduction in annualized relapse rate associated with the use of natalizumab. There is a direct correlation between the pre-study relapse rate (over either 1 year or 3 years) and the on-study relapse rate. This is true both in subjects who received natalizumab, and those who did not. Nevertheless, the percent reduction in relapse rate associated with natalizumab is relatively consistent across pre-study relapse rate categories.

The McDonald criteria (see Section 10.3, McDonald Diagnostic Criteria for MS) use various measures to assess whether or not a patient has MS. The two Phase 3 studies enrolled primarily subjects with McDonald category 1 data in support of the diagnosis. However, in spite of relatively small enrollment numbers for subjects who met diagnostic criteria other than category 1 evidence, the two studies suggest that the effect of natalizumab is present of subjects with category 2 evidence, and perhaps subjects with category 3 evidence, of MS. The sample numbers are too small to assess the natalizumab effect, if any, in subjects with McDonald criteria category 4 evidence of MS.

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**Table 12: Primary Efficacy Endpoint, Annualized Relapse Rate – MS-Related Subgroups**

	Study 1801					Study 1802				
	Natalizumab		Placebo		reduction (%)	Natalizumab		Placebo		reduction (%)
	n	relapse rate	n	relapse rate		n	relapse rate	n	relapse rate	
<b>Overall</b>	627	0.25	315	0.735	66.0%	245	0.253	265	0.687	63.2%
<b>Baseline EDSS</b>										
0	31	0.215	18	0.879	75.5%	24	0.068	19	0.659	89.7%
1	72	0.227	35	0.344	34.0%	45	0.212	35	0.79	73.2%
1.5	107	0.199	59	0.656	69.7%	101	0.305	108	0.733	58.4%
2	129	0.23	59	0.767	70.0%	130	0.383	124	0.796	51.9%
2.5	79	0.23	44	0.738	68.8%	83	0.441	79	0.641	31.2%
3	82	0.261	30	0.714	63.4%	76	0.362	63	0.847	57.3%
3.5	48	0.233	33	0.754	69.1%	49	0.331	64	0.921	64.1%
4	37	0.368	16	0.742	50.4%	42	0.442	48	0.746	40.8%
4.5	23	0.406	12	1.549	73.8%	26	0.579	23	0.887	34.7%
5 to 6	19	0.461	9	1.18	60.9%	13	0.33	19	0.875	62.3%
<b>Number of Relapses in Year Prior to Enrollment</b>										
0	6	0.167	6	0.722	76.9%	0	-	1	0	
1	368	0.219	180	0.623	64.8%	390	0.317	357	0.677	53.2%
2	197	0.287	102	0.74	61.2%	153	0.415	174	0.892	53.5%
3	43	0.284	20	1.65	82.8%	32	0.585	39	1.15	49.1%
≥ 4	13	0.468	7	0.94	50.2%	12	0.345	11	1.099	68.6%
<b>Number of Relapses in 3 Years Prior to Enrollment</b>										
1	105	0.155	49	0.421	63.2%	70	0.178	70	0.405	56.0%
2	206	0.17	125	0.607	72.0%	156	0.236	163	0.607	61.1%
3	168	0.304	82	0.77	60.5%	169	0.366	149	0.776	52.8%
4	79	0.345	32	1.16	70.3%	91	0.425	92	0.93	54.3%
≥ 5	69	0.389	27	1.29	69.8%	100	0.602	108	1.16	48.1%
<b>Baseline McDonald Criteria Classification</b>										
1	528	0.246	261	0.783	68.6%	538	0.367	532	0.789	53.5%
2	72	0.292	40	0.58	49.7%	46	0.266	44	0.752	64.6%
3	18	0.164	10	0.301	45.5%	3	0.217	3	0.334	35.0%
4	9	0.311	4	0.251	-23.9%	2	0	3	0	0.0%
<b>Received Approved Alternative MS Drug Prior to Enrollment *</b>										
Yes	48	0.461	26	0.936	50.7%	80	0.429	75	0.785	45.4%
No	579	0.232	289	0.717	67.6%	509	0.345	507	0.779	55.7%
<b>Number of Baseline Gadolinium-enhancing Lesions</b>										
0	311	0.234	172	0.57	58.9%	393	0.377	374	0.616	38.8%
1	117	0.22	52	0.74	70.3%	101	0.349	107	0.951	63.3%
2	63	0.272	26	0.783	65.3%	32	0.239	32	0.938	74.5%
3	38	0.276	18	0.566	51.2%	20	0.285	27	1.07	73.4%
4 to 9	63	0.282	30	1.27	77.8%	35	0.303	35	1.578	80.8%
10 to 98	35	0.36	17	1.56	76.9%	8	0.335	7	1.083	69.1%
<b>Number of Baseline T2 Hyperintense Lesions</b>										
< 9	31	0.363	16	0.563	35.5%	68	0.476	52	0.556	14.4%
≥ 9	596	0.244	299	0.745	67.2%	521	0.341	530	0.802	57.5%

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\* For Study 1801, the term "Approved Alternative MS Drug" in the above table refers to either glatiramer acetate or any beta interferon. For Study 1802, all subjects received Avonex<sup>®</sup> prior to the study, and the term "Approved Alternative MS Drug" in this table refers to either glatiramer acetate or any beta interferon other than Avonex<sup>®</sup>.

In general, subjects who had previously taken an alternative MS drug experienced higher relapse rates than subjects who had never taken an alternative MS drug. This is expected, given that patients with more active disease would be more likely to utilize a treatment for their MS than subjects with relatively inactive disease. However, the percent reduction in relapse rate was similar for these two groups of subjects.

In the placebo groups of both studies, there were trends toward higher relapse rates in subjects who had higher baseline numbers of gadolinium-enhancing lesions on MRI. Of note, however, the percent reduction in relapse rate associated with natalizumab administration tended to increase in subjects with higher numbers of baseline gadolinium-enhancing lesions, particularly in study 1802. Thus, the data do not suggest waning of natalizumab's treatment effect with greater baseline MRI activity.

In both studies, the natalizumab treatment effect was less robust in subjects with  $<9$  (versus  $\geq 9$ ) baseline numbers of T2 hyperintense lesions. There were trends in favor of lower relapse rates in the placebo groups, as well as higher relapse rates in the natalizumab groups. However, only ~5% and ~10% of subjects in Studies 1801 and 1802, respectively, had  $<9$  baseline T2 lesions at baseline, so some measure of caution is called for in interpreting these results.

Table 13 provides annualized relapse rates for each center that enrolled  $\geq 20$  subjects. There was a wide range in the percent reduction in annualized relapse rate. However, consistent with the robust natalizumab treatment effect observed across both studies, all but one of these larger enrolling sites showed a trend in favor of natalizumab.

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**Table 13: Primary Efficacy Endpoint, Annualized Relapse Rate, by Study Center**

	Study 1801					Study 1802				
	Natalizumab		Placebo		reduction (%)	Natalizumab		Placebo		reduction (%)
	n	relapse rate	n	relapse rate		n	relapse rate	n	relapse rate	
<b>Overall</b>	627	0.25	315	0.735	66.0%	245	0.253	265	0.687	63.2%
<b>Individual Large (≥ 20 Subjects) Centers</b>										
<b>1801 Site Number</b>										
108	21	0.178	11	0.551	67.7%					
313	14	0.406	7	1.654	75.5%					
322	13	0.562	7	0.628	10.5%					
402	14	0.205	7	1.645	87.5%					
403	13	0.63	7	1.171	46.2%					
405	13	0	7	0.266	100.0%					
407	13	0.067	7	0	-100.0%					
440	14	0.133	6	0.655	79.7%					
443	13	0.15	7	0.563	73.4%					
446	13	0.21	7	0.263	20.2%					
449	14	0	7	0.125	100.0%					
<b>1802 Site Number</b>										
125						12	0.235	12	0.463	49.2%
142						10	0.141	10	0.238	40.8%
151						13	0.265	14	1.352	80.4%
156						12	0.205	11	0.471	56.5%
168						15	0.133	16	0.937	85.8%
170						15	0.213	16	0.637	66.6%
176						10	0.581	10	0.777	25.2%
197						11	0.514	12	1.105	53.5%
952						10	0.636	10	0.824	22.8%

#### 6.1.4.6 Efficacy Results – Secondary Endpoints

The secondary endpoints were rank prioritized in the order presented below. If statistical significance ( $p < 0.05$ ) was not achieved for any secondary endpoint, all secondary endpoints of a lower rank were not considered statistically significant. Analysis of all MRI scans was performed at a central facility that was blinded to treatment assignment.

##### 6.1.4.6.1 New or Newly-enlarging T2 Hyperintense Lesions

This secondary endpoint was prespecified as the reduction in the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, comparing the natalizumab group to the

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placebo group, using a pre-specified logit regression, adjusted for baseline number of T2 lesions (<9 versus  $\geq 9$  lesions).

Table 14 includes only those subjects who had year 1 gadolinium-enhancing MRI data available.

<b>Table 14: Number of New or Newly-Enlarging T2 Hyperintense Lesions on Year 1 MRI*</b>				
	Study 1801		Study 1802	
	Placebo N = 293	Natalizumab N = 600	Placebo N = 485	Natalizumab N = 505
0	70 (24%)	376 (63%)	230 (47%)	392 (78%)
1	41 (14%)	112 (19%)	70 (14%)	69 (14%)
2	23 (8%)	40 (7%)	61 (13%)	24 (5%)
3	24 (8%)	30 (5%)	39 (8%)	10 (2%)
4-9	71 (24%)	34 (6%)	55 (11%)	8 (2%)
10-98	64 (22%)	8 (1%)	30 (6%)	2 (<1%)

\*Missing data omitted from analyses.

Considering subjects with available 1 year MRI data, natalizumab treatment was associated with absolute increases of 39% and 31% in the percentage of subjects with no new or newly-enlarging T2-hyperintense lesions in Studies 1801 and 1802, respectively (Table 14).

Subjects who are missing MRI data are likely to be a biased population. Therefore, the above analyses, which exclude these subjects, may over-represent the relative number of subjects in each group with a good outcome (i.e., a low number of new or newly-enlarging T2-hyperintense lesions).

Applicant's analysis: In Study 1801, Year 1 T2 MRI data are missing for 49 subjects: 22 in the placebo group and 27 in the natalizumab group. The mean number of new or newly-enlarging T2 hyperintense lesions at Year 1 was 2.85 for all subjects with Year 1 MRI data. This value was rounded to 3 and imputed as the number of new or newly enlarging T2 hyperintense lesions at Year 1 for all subjects who did not have a Year 1 MRI.

In Study 1802, Year 1 T2 MRI data is missing for 181 subjects: 97 in the placebo group and 84 in the natalizumab group. The mean number of new or newly-enlarging T2 hyperintense lesions at Year 1 was 1.30 for all subjects with Year 1 MRI data. This value was rounded to 1 and imputed as the number of new or newly enlarging T2 hyperintense lesions at Year 1 for all subjects who did not have a Year 1 MRI.

Using the above imputation for Study 1801, treatment with natalizumab resulted in an 80% reduction in the mean number of new or newly-enlarging T2-hyperintense lesions (6.1 vs. 1.2,  $p < 0.001$ , Table 15). Using the above imputation for Study 1802, treatment with natalizumab resulted in a 76% reduction in the mean number of new or newly-enlarging T2-hyperintense lesions (2.1 vs. 0.5,  $p < 0.001$ , Table 15). Because the numbers of lesions are not normally



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distributed (see Table 14), the median values and the distributions of subjects may be more representative of natalizumab activity than the mean values.

<b>Table 15: 1 Year New or Newly-Enlarging T2-Hyperintense Lesions</b>				
	Study 1801		Study 1802	
	Placebo N = 315	Natalizumab N = 627	Placebo + Avonex® N = 582	Natalizumab + Avonex® N = 589
Median	3	0	1	0
Range				
Mean	6.1	1.2	2.1	0.5
Standard Deviation	8.89	4.66	3.67	1.13

#### 6.1.4.6.2 Gadolinium-Enhancing Lesions

This secondary endpoint was prespecified as the reduction in the number of gadolinium-enhancing lesions on brain MRI scans, comparing the natalizumab group to the placebo group, using a pre-specified logit regression, adjusted for baseline number of gadolinium-enhancing lesions. For this analysis, missing values were imputed using the mean number of gadolinium-enhancing lesions in the study population.

Applicant's analyses: In Study 1801, there was a 92% reduction in the mean number of Gd-enhancing lesions (1.2 vs. 0.1,  $p < 0.001$ ). In Study 1802, there was an 88% reduction in the mean number of Gd-enhancing lesions (0.8 vs. 0.1,  $p < 0.001$ ; Table 16).

<b>Table 16: Summary of 1 Year Gadolinium-Enhancing Lesions</b>				
	Study 1801		Study 1802	
	Placebo N = 315	Natalizumab N = 627	Placebo N = 582	Natalizumab N = 589
Median	0	0	0	0
Range				
Mean	1.25	0.12	0.77	0.13
Standard Deviation	3.18	1.33	2.47	0.39

Because the numbers of lesions are not normally distributed (see Table 17), the median values and distributions of subjects may be more representative of natalizumab activity than the mean values. Table 17 includes only those subjects who had Year 1 gadolinium-enhancing MRI data available.

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<b>Table 17: Number of Gadolinium-Enhancing Lesions on Year 1 MRI</b>				
	Study 1801		Study 1802	
	Placebo N = 292	Natalizumab N = 600	Placebo N = 483	Natalizumab N = 504
0	192 (66%)	577 (96%)	343 (71%)	479 (95%)
1	41 (14%)	17 (3%)	71 (15%)	18 (4%)
2	15 (5%)	4 (1%)	27 (6%)	3 (1%)
3	8 (3%)	0 (0%)	13 (3%)	2 (<1%)
4-9	27 (9%)	1 (<1%)	21 (4%)	2 (<1%)
10-43	9 (3%)	1 (<1%)	8 (2%)	0 (0%)

In Study 1801, a single subject (subject #124-006) with gadolinium-enhancing lesions accounted for 50% of the 64 total gadolinium-enhancing lesions in all 600 natalizumab group subjects. Subject 124-006 is a 50 year-old woman who received 7 doses of natalizumab. She did not receive any natalizumab doses after Week 24, so she was off natalizumab for approximately 6 months before she had the MRI that showed gadolinium-enhancing lesions.

In subjects with 1 year MRI data available regarding the number of gadolinium-enhancing lesions (Table 17), natalizumab treatment resulted in a 30% absolute increase (45 % relative increase) in the percent of Study 1801 subjects with no gadolinium-enhancing lesions, and a 24% absolute increase (34 % relative increase) in the percent of Study 1802 subjects with no gadolinium-enhancing lesions. Most striking is the fact that 96% of natalizumab-treated subjects in Study 1801 had no gadolinium-enhancing lesions at one year, and this finding was precisely recapitulated in Study 1802.

Subjects who are missing MRI data are likely to be a biased population. Therefore, the above analyses, which exclude these subjects, may over-represent the relative number of subjects in each group with a good outcome (i.e., a low number of gadolinium-enhancing lesions).

In Study 1801, Year 1 MRI data regarding gadolinium-enhancing lesions are missing for 50 subjects: 23 in the placebo group and 27 in the natalizumab group. The mean number of gadolinium-enhancing lesions at Year 1 was 0.50 for all subjects with Year 1 MRI data. This value was imputed as the number of gadolinium-enhancing lesions at Year 1 for all Study 1801 subjects who did not have data regarding gadolinium-enhancing lesions at Year 1.

In Study 1802, Year 1 MRI data regarding gadolinium-enhancing lesions are missing for 184 subjects: 99 in the placebo group and 85 in the natalizumab group. The mean number of gadolinium-enhancing lesions at Year 1 was 0.45 for all subjects with Year 1 MRI data. This value was imputed as the number of gadolinium-enhancing lesions at Year 1 for all Study 1802 subjects who did not have data regarding gadolinium-enhancing lesions at Year 1.

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#### 6.1.4.6.3 Proportion of Subjects Relapse-Free

This secondary endpoint was prespecified as the increase in the proportion of relapse-free subjects, comparing the natalizumab group to the placebo group, using a pre-specified logistic regression adjusted for the number of relapses in the one year prior to study entry. For this analysis, a subject was considered to have relapsed if either the subject withdrew from the study and did not experience a relapse prior to withdrawal, or the subject took alternative MS medications and did not experience a relapse.

Applicant's analyses: In Study 1801, natalizumab was associated with a 43% relative (23% absolute) increase in the proportion of relapse-free subjects (76% vs. 53%,  $p < 0.001$ ). There are 32 subjects (13 subjects in the placebo group; 19 subjects in the natalizumab group) for whom relapse information is unknown, either because they left the study prior to having a relapse or because they started an alternative MS drug prior to having a relapse. In the applicant's analysis, all of these subjects are considered to have relapsed.

Table 18: Proportion of Subjects Relapse-Free						
	Study 1801			Study 1802		
	Placebo N = 315	Natalizumab N = 627	Relative risk <sup>0</sup> (95% CI)	Placebo + Avonex <sup>®</sup> N = 582	Natalizumab + Avonex <sup>®</sup> N = 589	Relative risk <sup>0</sup> (95% CI)
Number relapse- free <sup>1</sup>	166 (53%)	474 (76%)	1.43 (1.28, 1.61)	265 (46%)	392 (67%)	1.46 (1.32, 1.62)
Number relapse- free <sup>2</sup>	N = 302	N = 608	1.42 (1.27, 1.58)	N = 563	N = 569	1.46 (1.32, 1.62)
	166 (55%)	474 (78%)		265 (47%)	392 (69%)	
Number relapse- free <sup>3</sup>	N =299	N = 597	1.32 (1.19, 1.48)	N =582	N = 589	1.36 (1.23, 1.51)
	171 (57%)	452 (76%)		284 (49%)	392 (67%)	

<sup>0</sup> Relative risk of being relapse-free, comparing natalizumab group to placebo group

<sup>1</sup> Analysis with subjects of unknown status (including 13 placebo group and 19 natalizumab group subjects in Study 1801, 19 placebo group and 20 natalizumab group subjects in Study 1802) as having relapses (i.e., applicant's analysis)

<sup>2</sup> Analysis with subjects of unknown status excluded from the analysis

<sup>3</sup> Analysis with subjects of unknown status, using a worst-case possibility, counting placebo group subjects as not having a relapse and natalizumab group subjects as having a relapse; this analysis excluded data from all sites with a known conflict of interest (results in excluding 16 placebo subjects and 30 natalizumab subjects from the analysis).

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Reviewer's comment: The analyses in Table 18 indicate that the benefit seen with natalizumab is a robust effect that is not dependent on the method for imputation of missing data.

#### 6.1.5 Clinical Microbiology

Natalizumab is not an antimicrobial. Therefore, this section is not applicable to this review.

#### 6.1.6 Efficacy Conclusions

Analyses of the primary and secondary endpoints provide statistically strong and consistent support for the efficacy of natalizumab. Subgroup and sensitivity analyses also support the existence of a favorable treatment effect of natalizumab.

Natalizumab appears to be effective in decreasing the relapse rate at one year in subjects with active relapsing-remitting MS. Natalizumab is effective when administered as monotherapy and when administered as add-on therapy to a beta-interferon for subjects who have continued to relapse while taking Avonex®.

For other MS products, FDA has required two-year data to support an indication for decreasing the frequency of clinical relapses. A salutary effect on relapse rate at one year is not a validated surrogate for benefit at two years. However, the apparent treatment effect of natalizumab with respect to relapse rate at one year is unprecedented in the MS field, and its magnitude is reasonably likely to predict clinically meaningful effectiveness at two years. If, in fact, the benefit on clinical relapses is shown to be durable through two years, the product may be substantially more efficacious than currently approved MS therapies (see Section 2.2, Currently Available Treatment for Indications).

It is possible, however, that the magnitude of natalizumab's effect on relapse rate, when assessed through one year, may substantially overestimate natalizumab's benefit on relapse rate through two years, as well as its risks. In particular, the treatment effect appears to wane with the development of anti-natalizumab antibodies, which may increase with time (see Section 7.1.10, Table 34). Therefore, the final two-year results of the two Phase 3 studies (Studies 1801 and 1802) are critical for a more complete characterization of the risk benefit relation (see Section 9.3.2, Required Phase 4 Commitments).

The effect of natalizumab as an add-on therapy appears to represent a significant advance over currently available first-line MS treatments (the interferon betas and glatiramer acetate), none of which have proven efficacy as add-on therapy to one another (see Section 2.2, Currently Available Treatment for Indications). Therefore, natalizumab has the potential to address an unmet medical need by providing a benefit when added to an existing therapy.

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## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

The total exposure to natalizumab in placebo-controlled MS and CD trials (see Section 4.2, Tables of Clinical Studies) is outlined in Table 19. Table 19 includes the data from a 120-day safety update (Amendment 12 to the original BLA application), which includes Study 1801 safety data through March 1, 2004 and Study 1802 safety data through April 15, 2004.

The table highlights the limited duration of exposure to natalizumab in CD placebo-controlled trials, relative to the MS trials. Study CD303 is a moderately-sized (428 subjects), placebo-controlled study of administration of the proposed recommended natalizumab dose for up to 48 weeks in subjects with CD. Study CD303 is ongoing and therefore provides limited data for this review. The open-label experience in CD includes exposure of 1098 subjects to natalizumab, but includes only 382 subjects with at least one year of exposure to natalizumab. The placebo-controlled experience in normal volunteers is limited to the 35 subjects in Study 101. Phase 1 and Phase 2 studies of natalizumab in MS were generally small, brief in duration, and/or used weight-adjusted natalizumab dosing (see Section 4.2, Tables of Clinical Studies). For these reasons, the studies in CD, ulcerative colitis (a single open-label study in 10 subjects), and normal volunteers, as well as the Phase 1 and Phase 2 MS studies, do not contribute substantially to the safety database, and are not considered in detail in this review.

**Table 19: Total Exposure to Natalizumab in Placebo-Controlled Trials**

	Multiple Sclerosis			Crohn's Disease		
	Total	Natalizumab	Placebo	Total	Natalizumab	Placebo
Total N	2752	1617	1135	1178	922	256
Duration of Exposure (weeks)						
1 to <12	376	247	129	1178	922	256
12 to <24	114	63	51	0	0	0
24 to <52	331	184	147	0	0	0
52 to <116	1924	1119	805	0	0	0
≥ 116	7	4	3	0	0	0

Thus, this safety review is based primarily on the experience in Studies 1801 and 1802 (see Section 6.1.3, Study Design), which are the only large, placebo-controlled clinical trials that administered the proposed recommended dose of natalizumab (300 mg IV every 4 weeks) to MS subjects for more than 6 months. Study 1801 compared natalizumab monotherapy (627 subjects) to placebo (315 subjects) and is highlighted in this safety review. Study 1802 included administration of natalizumab (582 subjects) or placebo (589 subjects) to subjects who also received Avonex® 30 µg IM once a week. Because all subjects in Study 1802 received background administration of Avonex®, Study 1802 provides a less clear assessment of the

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safety of natalizumab, compared to Study 1801. **Thus, the Study 1801 data were primarily used to assess the incidence of adverse events against a placebo background.**

For ongoing studies, including MS trials 1801, 1802, and 1808, and CD trials CD303, CD351, and CD352, this review considers safety data through cut-off dates ranging from March 1<sup>st</sup> to April 30<sup>th</sup>, 2004.

#### 7.1.1 Deaths

There have been nine deaths in the natalizumab development program. The causes of death are summarized below:

- Three subjects receiving placebo in MS trials
  1. 66 year-old woman – pleural carcinomatosis complicated by hemothorax and myocardial infarction, Study 231
  2. 47 year-old woman – sudden death, presumed cardiac arrhythmia, Study 1802
  3. 23 year-old woman – sudden death, unexplained, Study 1802
- Two subjects receiving natalizumab in MS trials
  1. 49 year-old woman – violent death (homicide or suicide; police investigation in progress), Study 1801
  2. 5 year-old girl – respiratory distress secondary to progressive MS, Study 1804; At age 18 months, while recovering from a fever and upper respiratory infection, the subject developed a right hemiparesis. Subsequent exacerbations included transverse myelitis, truncal ataxia, bilateral optic neuritis, and left hemiparesis. She did not tolerate cyclophosphamide and did not respond adequately to steroids, intravenous immunoglobulin, and a beta-interferon. The sponsor initiated a single-subject study in order to provide her with open-label natalizumab. She received a total of ten weight-adjusted (3 mg/kg – 6 mg/kg) infusions of natalizumab. She received her last natalizumab infusion on However, due to continued progression of her MS, natalizumab administration was discontinued. She was subsequently treated with mitoxantrone and daclizumab. In she was blind as a result of MS and had a white blood cell count of 500/mm<sup>3</sup>. She died in with cause of death listed as MS and post-infectious encephalitis.
- Four subjects receiving natalizumab in CD trials
  1. 42 year-old man – carbon monoxide poisoning, described by the applicant as “work-related ... [and] accidental,” Study 301
  2. 49 year-old woman – progression of CD and nephrotic syndrome, complicated by peritonitis and sepsis, Study 301
  3. 60 year-old man – malignant astrocytoma, Study 351
  4. 73 year-old man – perforated duodenal ulcer with peritonitis and pulmonary aspergillosis, Study 351

The deaths in MS trials do not provide a clear safety signal, although the possibility of a suicide in a Study 1801 subject who received natalizumab is of concern. The deaths in CD trials are of concern, particularly because a mechanistic relationship to natalizumab is plausible for the two



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subjects who developed infections and the one subject who developed a malignancy (see Section 2.4, Important Issues With Pharmacologically Related Products).

#### 7.1.2 Non-Fatal Serious Adverse Events

Table 20 provides the applicant's analysis of serious adverse events from all placebo-controlled trials in MS and CD. Note that with the exception of hypersensitivity and anaphylactoid reactions, no safety signal emerges.

In its examination of the adverse event listings, CDER found a number of events that had been divided into multiple categories, making their detection difficult (e.g., "pneumonia," "lobar pneumonia," "atypical pneumonia," etc.). Thus, CDER performed a manual, blinded analysis of the adverse event listings in the safety "as treated" population. This involved tabulation of 31,278 lines of adverse event data for Studies 1801 and 1802. Adverse events which occurred prior to the first administration of study agent were not considered in this analysis.

Table 21 summarizes CDER's analysis, which includes all serious adverse events with an incidence  $>0.5\%$  in the natalizumab group in Studies 1801 and 1802 (see Section 2.4, Important Issues With Pharmacologically Related Products). Note that the numbers can not be compared to the applicant's analyses in Table 20, because the applicant has combined Studies 1801 and 1802 with other MS studies under the "Multiple Sclerosis" columns (left).

<b>Table 20: Percent of Subjects with Serious Adverse Events in Placebo-Controlled Trials; Includes All Serious Adverse Events With Incidence <math>\geq 1\%</math> In Natalizumab Group, And Selected Serious Adverse Events of Interest (From Applicant's Analysis)</b>				
(%)	Multiple Sclerosis <sup>1</sup>		Crohn's Disease <sup>2</sup>	
	Natalizumab N = 1617	Placebo N = 1135	Natalizumab N = 922	Placebo N = 256
Any serious adverse event	12.5	15.2	17.4	17.2
Infections and infestations	1.8	1.6	2.8	3.1
Neoplasms	0.6	1.2	0.9	0.4
Hypersensitivity / Anaphylactoid	0.7	0.2	0.5	0.4
Depression / Suicide attempt	0.6	0.7	0.2	0.8
Cardiac disorders	$<0.1$	0.4	0.5	0

<sup>1</sup> Placebo-controlled MS trials includes studies 200, 202, 221, 201, 231, 1801, 1802, and 1803

<sup>2</sup> Placebo-controlled CD studies include CD 1801, CD202, and CD301



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**Table 21: CDER Analysis of Serious Adverse Events, >0.5% Incidence in Study 1801, Greater Frequency in Natalizumab Group Than Placebo Group**

	Study 1801		Study 1802	
	Natalizumab	Placebo	Natalizumab + Avonex	Placebo + Avonex
	n = 627	n = 315	n = 601	n = 595
Infection	13 (2.1%)	4 (1.3%)	11 (1.8%)	7 (1.2%)
Allergic reaction	8 (1.3%)	1 (0.3%)	2 (0.3%)	3 (0.5%)
Anaphylaxis	3 (0.5%)	0 (0%)	1 (0.2%)	1 (0.2%)
Cholelithiasis	5 (0.8%)	1 (0.3%)	2 (0.3%)	0 (0%)
Depression	5 (0.8%)	3 (1.0%)	2 (0.3%)	1 (0.2%)
Suicidal Ideation or Attempt	3 (0.5%)	1 (0.3%)	0 (0%)	1 (0.2%)
Neoplasm	4 (0.6%)	1 (0.3%)	3 (0.5%)	5 (0.8%)
Urinary Tract Infection	4 (0.6%)	1 (0.3%)	2 (0.3%)	1 (0.2%)
Pneumonia	4 (0.6%)	0 (0%)	1 (0.2%)	1 (0.2%)

Notable serious adverse events, more frequent in the natalizumab group, were infection (including pneumonia and urinary tract infection), allergic reaction, anaphylaxis, and cholelithiasis.

Of note, the majority of subjects were exposed to the study agent for less than 13 months. The total number of adverse events per subject will increase with the two-year exposure in the two Phase 3 studies. Therefore, the final study reports for those studies will provide a more complete picture of the adverse event profile.

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall Profile of Dropouts

The total number of dropouts (approximately 4% in Study 1801 and 6% in Study 1802) at one year is well within the range of other large MS trials (

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Table 22). MS patients now have several available treatment options (see Section 2.2, Immune Modulators Approved for Treatment of MS). Study subjects in current trials may be less tolerant of adverse events or perceived lack of efficacy than during previous trials when treatment options were more limited. Dropouts due to lack of efficacy were more common in the placebo group in each study, consistent with natalizumab's association with decreased relapse rate. Dropouts due to adverse events were similar in the two groups in each study. However, dropouts due to allergic reactions (including hypersensitivity reactions and urticaria) were more common in the natalizumab group in Study 1801, consistent with clinically important immunogenicity of natalizumab (See Section 7.1.10, Immunogenicity).

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**Table 22: Dropouts from Pivotal Clinical Trials (CDER Analysis)\*\***

	Study 1801		Study 1802	
	Natalizumab N = 627	Placebo N = 315	Natalizumab + Avonex N = 589	Placebo + Avonex N = 582
<b>Total withdrawals from study (%)</b>	<b>21 (3)</b>	<b>8 (6)</b>	<b>29 (5)</b>	<b>41 (7)</b>
Withdrew consent prior to the first administration of study drug	0	3	0	0
<b>Total of adverse events</b>	<b>1</b>	<b>1</b>	<b>4</b>	<b>1</b>
Lack of efficacy and/or decision to take alternative MS therapy	1	4	5	17
<b>Subjects dropped from area</b>	<b>1</b>	<b>1</b>	<b>4</b>	<b>1</b>
Study procedures burdensome	0	1	3	6
<b>Pregnancy or unwilling to practice contraception</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>
Personal reasons or reason not specified	1	0	2	4
<b>Lost to follow-up</b>	<b>0</b>	<b>2</b>	<b>2</b>	<b>1</b>
Noncompliance	1	0	1	1
<b>Total study withdrawals due to adverse events (%)</b>	<b>19 (2)</b>	<b>6 (2)</b>	<b>8 (1)</b>	<b>6 (1)</b>
Urticaria	4	2	0	0
<b>Hypersensitivity reactions (includes anaphylaxis and anaphylactoid reactions)</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>
Abdominal pain	1	0	0	0
<b>Adverse drug reaction, not otherwise specified</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>
Conjunctivitis, night sweats, arthralgia, and headache	1	0	0	0
<b>Alcohol poisoning</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>
Cough	1	0	0	0
<b>Allergic dermatitis</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>
Overdose, not otherwise specified	1	0	0	0
<b>Depression or suicidal ideation</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>1</b>
Ulcerative colitis	0	1	0	0
<b>Elevated liver function tests</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>
Multiple sclerosis	0	1	1	1
<b>Myeloskeletal stiffness</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>
Rash, not otherwise specified	0	1	0	0
<b>Diarrhea</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>0</b>
Headache	0	0	1	0
<b>Herpes zoster</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>
Nasopharyngitis	0	0	1	0
<b>Peripheral edema</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
Pain in extremity	0	0	1	0
<b>Fever</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>
Syncope	0	0	1	0
<b>Breast cancer</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Death, presumed cardiac etiology	0	0	0	1
<b>Increased flu-like symptoms</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Molluscum contagiosum	0	0	0	1

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\* Some subjects cited more than one adverse event as reason for withdrawal from the study.

\*\* Includes only dropouts through the date of the 1-year analysis (see Section 6.1.2, General Discussion of Endpoints).

#### 7.1.3.2 Adverse Events Associated With Dropouts

In the two Phase 3 MS studies, the most common adverse events associated with dropping out of the study or discontinuing study medication were urticaria, anaphylaxis, and hypersensitivity reactions (see Section 7.1.10, Immunogenicity), and depression or suicidal ideation. Each of these types of events occurred more frequently in subjects who received natalizumab (see Section 7.1.5, Common Adverse Events).

#### 7.1.3.3 Other Significant Adverse Events

All significant adverse events are listed as either serious adverse events (see Section 7.1.2, Other Serious Adverse Events), or reasons for discontinuation of treatment (see Section 7.1.3.1, Overall profile of dropouts). Significant laboratory abnormalities are discussed in Section 7.1.7.3, Standard analyses and explorations of laboratory data).

#### 7.1.4 Other Search Strategies

On request of CDER, the applicant provided tables listing the frequency of adverse events relative to the time of study agent infusion. The objective of this analysis was to look for distribution patterns that differed between the two arms of the studies. For example, events that relate to a relatively high concentration of natalizumab might be more likely to cluster in the natalizumab group, but not in the placebo group, in the first few days following study agent administration. Similarly, CDER reviewed data for Studies 1801 and 1802, separately and combined. CDER did not identify any clear difference in the pattern of distribution of events.

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting Adverse Events Data in The Development Program

The applicant's approach to eliciting adverse event data was the same in Studies 1801 and 1802, the two pivotal studies.

An adverse event was defined as any untoward medical occurrence experienced by a subject. An adverse event could be any sign (including an abnormal laboratory result that the investigator determined was clinically significant), symptom, or diagnosis/disease that was unfavorable or unintended, that appeared or worsened in a subject. All adverse events reported by the subject or observed by investigational site personnel from the start of study drug treatment until (and including) the subject's last follow-up visit were recorded in the subject's case report form (CRF). Laboratory values that were deemed clinically significant were recorded as adverse

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events. Adverse events were to be recorded regardless of relationship to study drug. Adverse events reported solely at the screening visit (prior to administration of the test agent) were not included in the analyses.

Overdose and pregnancy were not considered adverse events, although the applicant did collect this information. However, if there were subsequent adverse events as a result of overdose or pregnancy, these subsequent events were to be reported on the adverse event form.

Adverse Events were classified as serious if they met any of the following criteria (in accordance with 21 CFR Part 312.32).

- Any death.
- Any life-threatening event, i.e., an event that placed the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (does not include an event that, had it occurred in a more severe form, might have caused death).
- Any event that required or prolonged in-patient hospitalization.
- Any event that resulted in persistent or significant disability/incapacity.
- Any congenital anomaly/birth defect diagnosed in a child of a subject who was participating in this study and received study drug.
- Other medically important events that in the opinion of the investigator jeopardized the subject or required intervention to prevent one of the other outcomes listed in the definition above.
- A new diagnosis of cancer.

Monitoring and recording of adverse events were performed at each study visit after randomization. This included Study Drug Administration Visits (SDAVs) at baseline (Week 0) and every 4 weeks (+/- 3 days) through Week 116, Unscheduled Clinical Evaluation Visits (CEVs) to assess possible relapses, an End-of-Study visit at Week 120, and a post-treatment visit at Week 128. For subjects who discontinued study agent administration, telephone contacts every four weeks to monitor adverse events replaced the SDAVs. For subjects who dropped out of the study, adverse events were recorded at a premature study withdrawal visit. Additional information regarding the assessments at each visit is provided in Section 6.1.3.1.4, Study 1801 – Study Procedures.

#### 7.1.5.2 Appropriateness of Adverse Event Categorization and Preferred Terms

The applicant provided COSTART and MedDRA terms for all adverse events in the two Phase 3 MS trials. CDER initially disagreed with the applicant on the classification of some adverse

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events. CDER reviewed the primary symptom for each adverse event and classified each adverse event as deemed appropriate, with no consideration for the COSTART and MedDRA classification provided by the applicant. CDER did not conduct any formal assessment of the extent of disagreement between the applicant's classification and CDER's classification of adverse events. However, CDER and the applicant resolved all substantial disagreements through extensive discussion and cooperative review of the safety database. Examples of initial disagreements included: separation of loss of consciousness from syncope (CDER considered both together), separation of "lobar pneumonia," "bronchial pneumonia," and "atypical pneumonia," (CDER considered all as "pneumonia"), etc. Agreement was reached to use gender-specific denominators for gender-related adverse events, e.g., gynecologic events.

#### 7.1.5.3 Incidence of Common Adverse Events

This safety review is based on CDER's independent classification of adverse events. For reasons discussed previously (see Section 7.1, Methods and Findings), the adverse event tables in the next section consider only adverse events from Studies 1801 and 1802.

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#### 7.1.5.4 Common Adverse Event Tables

Table 23 summarizes CDER's analyses of common adverse events from Studies 1801 and 1802, based on a blinded classification of the 31,278 line listings. The table includes events with a frequency of  $\geq 2\%$  in study 1801.

**Table 23: Common Adverse Events With Incidence of  $\geq 2\%$  in Natalizumab Group of Study 1801**

	Study 1801		Study 1802	
	Natalizumab n=627	Placebo n=315	Natalizumab + Avonex n=601	Placebo + Avonex n=595
infection	424 (67.6)	198 (62.9)	236 (39.3)	242 (40.7)
headache	206 (32.9)	92 (29.2)	147 (24.5)	142 (23.9)
fatigue or malaise	149 (23.8)	57 (18.1)	105 (17.5)	114 (19.2)
depression	106 (16.9)	43 (13.7)	65 (10.8)	53 (8.9)
arthritis/arthralgia	105 (16.7)	38 (12.1)	85 (14.1)	75 (12.6)
sleep disorder	90 (14.4)	38 (12.1)	73 (12.1)	63 (10.6)
urinary tract infection	89 (14.2)	38 (12.1)	55 (9.2)	66 (11.1)
rhinitis, congestion stuffiness	80 (12.8)	36 (11.4)	54 (9)	41 (6.9)
abdominal discomfort	70 (11.2)	31 (9.8)	39 (6.5)	36 (6.1)
rash	58 (9.3)	22 (7)	36 (6)	39 (6.6)
gastroenteritis	55 (8.8)	16 (5.1)	51 (8.5)	42 (7.1)
urinary urgency and incontinence	53 (8.5)	15 (4.8)	43 (7.2)	37 (6.2)
infection, viral	51 (8.1)	22 (7)	47 (7.8)	46 (7.7)
* vaginitis	32 (7.1)	8 (3.8)	20 (4.5)	28 (6.7)
* menstrual irregularities	30 (6.7)	7 (3.4)	15 (3.4)	9 (2.1)
GOT/GPT/GGT	30 (4.8)	10 (3.2)	14 (2.3)	20 (3.4)
dermatitis	27 (4.3)	9 (2.9)	23 (3.8)	11 (1.8)
pruritus	25 (4)	6 (1.9)	19 (3.2)	17 (2.9)
allergic reaction	23 (3.7)	4 (1.3)	14 (2.3)	18 (3)
rigors	17 (2.7)	3 (1)	15 (2.5)	2 (0.3)
bleeding	17 (2.7)	5 (1.6)	8 (1.3)	7 (1.2)
* dysmenorrhoea	11 (2.4)	1 (0.5)	8 (1.8)	16 (3.8)
neuralgia	10 (1.6)	1 (0.3)	7 (1.2)	5 (0.8)
* amenorrhea	8 (1.8)	0 (0)	0 (0)	4 (1.0)

\* percentage based on female n



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Table 24 includes all severe adverse events with incidence of at least 0.6% in the natalizumab group in Study 1801 (see Section 2.4, Important Issues With Pharmacologically Related Products). The most concerning signal is infection, although most were mild and resolved either spontaneously or to usual antibiotic intervention. The incidence of severe adverse events was generally low in this study, for an MS population.

**Table 24: Severe Adverse Events with Incidence  $\geq 0.6\%$  in Natalizumab Group (Study 1801)**

	Study 1801		Study 1802	
	Natalizumab n = 627	Placebo n = 315	Natalizumab + Avonex n = 601	Placebo + Avonex n = 595
infection	22 (3.5%)	8 (2.5%)	35 (5.8%)	29 (4.9%)
fatigue or malaise	19 (3%)	9 (2.9%)	22 (3.7%)	23 (3.9%)
MS possible relapses	19 (3%)	23 (7.3%)	10 (1.7%)	31 (5.2%)
headache	12 (1.9%)	11 (3.5%)	21 (3.5%)	16 (2.7%)
muscle cramp, spasm, stiffness, tightness, heaviness	9 (1.4%)	7 (2.2%)	12 (2%)	20 (3.4%)
mood or emotional disorders	8 (1.3%)	5 (1.6%)	12 (2%)	5 (0.8%)
back strain/ache	7 (1.1%)	3 (1%)	3 (0.5%)	12 (2%)
pain in extremity	6 (1%)	2 (0.6%)	6 (1%)	9 (1.5%)
infection, bacterial	5 (0.8%)	3 (1%)	4 (0.7%)	3 (0.5%)
sleep disorder	5 (0.8%)	1 (0.3%)	2 (0.3%)	3 (0.5%)
Arthritis/arthritis	5 (0.8%)	2 (0.6%)	6 (1%)	2 (0.3%)
miscellaneous allergic reaction	4 (0.6%)	1 (0.3%)	0 (0%)	2 (0.3%)
anaphylaxis /anaphylactoid	4 (0.6%)	0 (0%)	0 (0%)	1 (0.2%)
migraine	4 (0.6%)	3 (1%)	5 (0.8%)	11 (1.8%)
neoplasm	4 (0.6%)	0 (0%)	1 (0.2%)	2 (0.3%)
urinary tract infection	4 (0.6%)	1 (0.3%)	7 (1.2%)	4 (0.7%)
depression	4 (0.6%)	2 (0.6%)	10 (1.7%)	3 (0.5%)
anxiety	4 (0.6%)	2 (0.6%)	1 (0.2%)	0 (0%)

The incidence of Avonex<sup>®</sup> injection site reactions, including bruising, pain, and erythema, was approximately 3% in each study group of Study 1802. This low incidence probably reflects the study eligibility requirement that all subjects must have received Avonex<sup>®</sup> for at least one year prior to enrollment. MS patients who had Avonex<sup>®</sup> injection site reactions after prolonged exposure would most likely have discontinued Avonex<sup>®</sup> and been ineligible for Study 1802.

#### 7.1.5.5 Common and Drug-Related Adverse Events

See Table 23 and Table 24.

Adverse events that were more common in the natalizumab group include infection (including pneumonia), headache, fatigue or malaise, depression, other mood or emotional disorders, arthritis/arthritis, rhinitis and nasal congestion, ear and hearing disorders, abdominal

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discomfort, gastroenteritis, menstrual disorders (including menstrual irregularities, dysmenorrhea, and amenorrhea), dermatitis, bleeding (including epistaxis), urticaria, and hypersensitivity reactions (including anaphylaxis and anaphylactoid reactions). Most of these adverse events occurred with an incidence only slightly (i.e., 1-3%) higher in the natalizumab group than the placebo group in one or both of the two Phase 3 MS studies.

Of the many possible sites for infection, the most consistent site for an increased risk of infection associated with natalizumab was the gastrointestinal tract, with increased incidence of gastroenteritis in the natalizumab group in both studies. This is consistent with the proposed mechanism of action of natalizumab (see Section 2.1, Product Information), which binds to  $\alpha 4$ -integrins. The  $\alpha 4\beta 7$  integrin, which is expressed on lymphocytes with a tropism for the gastrointestinal tract, binds to the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Natalizumab may block this interaction by binding to the  $\alpha 4$  subunit, preventing the lymphocytes from reaching their normal targets in the gastrointestinal parenchyma. However, the clinical assessment of infection as the etiology of gastroenteritis can be difficult; therefore, this correlation of the proposed mechanism of action with the adverse event profile may be a spurious finding.

Infusion reactions were defined as adverse events that started within two hours after the initiation of the study drug infusion. In Study 1801, infusion reactions occurred in 20% of the natalizumab group subjects and 15% of the placebo group subjects. In Study 1802, infusion reactions occurred in 21% of the natalizumab group subjects and 16% of the placebo group subjects. The most common infusion reactions were headache, nausea, flushing, erythema, fatigue, dizziness, urticaria, pruritus, rigors, and chest tightness or pain. Headache occurred in 3-4% of subjects in Studies 1801 and 1802; all other infusion site reactions occurred in no more than 1% of subjects in either treatment group in either study. Infusion reactions that were classified as severe or serious included hypersensitivity reactions, dizziness, flushing, and headache; each of these severe or serious infusion reactions had an incidence <0.5%, except for hypersensitivity reactions, which occurred in the natalizumab groups with an incidence of 1%.

There were 4 malignancies reported in the natalizumab group in Study 1801 (0.6%) and 1 malignancy reported in the placebo group (0.3%). In Study 1802, there were 3 and 4 malignancies reported in the natalizumab + Avonex<sup>®</sup> and placebo + Avonex<sup>®</sup> groups, for rates of 0.5% and 0.7%, respectively. Overall, there was no clear association between natalizumab administration and malignancy.

#### 7.1.5.6 Additional Analyses and Explorations

Additional exploratory analyses of the adverse events that appeared to be drug-related centered on the issue of immunogenicity (see Section 7.1.10, Immunogenicity).

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#### 7.1.6 Less Common Adverse Events

##### 7.1.6.1 Uncommon Adverse events

CDER review of uncommon adverse events in the entire safety database did not identify additional safety concerns.

##### 7.1.6.2 Progression of Disability

The two primary clinical manifestations of multiple sclerosis are relapses and progression of disability (see Section 2, Introduction and Background). CDER expressed concern that natalizumab might produce a favorable effect on relapse frequency while having an adverse effect on progression of disability. However, progression of disability is the primary endpoint for the two-year analysis (see Section 6.1.2, General Discussion of Endpoints). In order to prevent any unblinding that might create bias in the study personnel, the applicant did not conduct any analyses of disability progression as part of the 1 year analyses in the original submission of this BLA. For the purpose of this BLA review, CDER viewed the progression of disability as solely a safety issue, and not as an efficacy parameter. CDER evaluated minimal information on disability in order to obtain some reassurance that natalizumab was not associated with an adverse effect on progression of disability. This information is viewed as safety data and does not impact the alpha allotment for the primary endpoint of progression of disability at two years (see Section 6.1.2, General Discussion of Endpoints). The limited data on disability did not reveal any apparent acceleration of disability in the natalizumab group.

#### 7.1.7 Laboratory Findings

##### 7.1.7.1 Overview of Laboratory Testing in the Development Program

For reasons discussed previously (see Section 7.1, Methods and Findings), this review focuses on laboratory testing in Studies 1801 and 1802. These two Phase 3 MS studies included the following laboratory studies.

- 1) Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen, creatinine, and bicarbonate at Screening, at Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, and at premature study withdrawal visits.
- 2) Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, total leukocyte (WBC) count (with differential), and platelet count at Screening, at Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, and at premature study withdrawal visits.

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- 3) Urinalysis: color, specific gravity, pH, protein, glucose, blood, and ketones at Screening, at Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, and at premature study withdrawal visits.

#### 7.1.7.2 Selection of Studies and Analyses for Drug-Control Comparisons of Laboratory Values

This review focuses on Studies 1801 and 1802, which provide the only substantial database on natalizumab exposure for at least 12 months. For further discussion of the selection of these two studies for analysis, see Section 7.1, Methods and Findings).

#### 7.1.7.3 Standard Analyses and Explorations of Laboratory Data

Natalizumab binds to the  $\alpha 4$  subunit of the  $\alpha 4 \beta 1$  integrin that is highly expressed on the surface of all leukocytes, with the exception of neutrophils (see Section 2.1, Product Information). Therefore, the following analyses focus on hematologic measures.

##### 7.1.7.3.1 Analyses Focused on Measures of Central Tendency

The applicant provided an analysis of laboratory measures based on central tendency, combining data from all placebo-controlled MS studies, including Studies 200, 202, 221, 201, 231, 1801, 1802, and 1803.

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<b>Table 25: Hematology Laboratory Measures, Baseline and Week 48 (mean)</b>		
Laboratory Measure	Natalizumab	Placebo
WBC ( $\times 10^9/L$ )		
Baseline (n)	6.9 (1573)	6.8 (1112)
Week 48 (n)	<b>8.5</b> (1184)	6.8 (819)
Lymphocytes ( $\times 10^9/L$ )		
Baseline (n)	2.0 (1573)	2.0 (1112)
Week 48 (n)	<b>3.3</b> (1182)	1.9 (818)
Neutrophils ( $\times 10^9/L$ )		
Baseline (n)	4.3 (1573)	4.3 (1112)
Week 48 (n)	4.3 (1182)	4.3 (818)
Monocytes ( $\times 10^9/L$ )		
Baseline (n)	0.39 (1573)	0.38 (1112)
Week 48 (n)	<b>0.49</b> (1182)	0.40 (818)
Eosinophils ( $\times 10^9/L$ )		
Baseline (n)	0.13 (1573)	0.13 (1112)
Week 48 (n)	<b>0.24</b> (1182)	0.13 (818)
Basophils ( $\times 10^9/L$ )		
Baseline (n)	0.046 (1573)	0.046 (1112)
Week 48 (n)	<b>0.064</b> (1182)	0.045 (818)
RBC ( $\times 10^{12}/L$ )		
Baseline (n)	4.6 (1573)	4.6 (1112)
Week 48 (n)	4.6 (1184)	4.7 (819)
Hemoglobin (g/dL)		
Baseline (n)	13.9 (1573)	14.0 (1112)
Week 48 (n)	13.5 (1184)	13.9 (819)
Hematocrit (%)		
Baseline (n)	41.7 (1564)	41.8 (1108)
Week 48 (n)	40.4 (1180)	41.9 (814)
MCV ( $\times 10^{15} L$ )		
Baseline (n)	90.7 (1564)	90.5 (1108)
Week 48 (n)	89.0 (1180)	89.8 (814)
Platelets ( $\times 10^9/L$ )		
Baseline (n)	271 (1565)	268 (1107)
Week 48 (n)	261 (1175)	267 (811)

As expected, considering its mechanism of action, natalizumab administration is associated with increases in total white blood cells, lymphocytes, monocytes, eosinophils, and basophils (**bold font**). These increases in non-neutrophil WBCs are associated with a decrease in the percent of neutrophils in the total WBC, although natalizumab is not associated with a change in the

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absolute neutrophil count. Natalizumab is associated with small mean decreases in hemoglobin, hematocrit, MCV, and platelets (Table 25). No changes are apparent in the placebo subjects.

#### 7.1.7.3.2 Analyses Focused on Outliers or Shifts From Normal to Abnormal

**Table 26: Laboratory Measures – Shifts to Abnormal (% of Subjects), 1-Year Analysis**

	Study 1801				Study 1802 (All + Avonex)			
	Shift to Low		Shift to High		Shift to Low		Shift to High	
	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab	Placebo
<b>Hematology</b>								
WBC	<1	2	38	15	2	9	26	7
Neutrophils	3	3	17	16	9	12	12	10
Lymphocytes	<1	<1	38	3	<1	6	29	1
Monocytes	<1	2	6	2	1	3	9	1
Eosinophils	0	0	13	4	0	0	10	2
Basophils	0	0	5	1	0	0	5	<1
RBC	23	8	0	<1	25	12	0	12
MCV	3	4	3	8	4	4	4	4
MCH	1	2	<1	<1	2	3	<1	3
MCHC	4	6	0	<1	3	5	0	5
Hemoglobin	8	3	0	1	12	7	0	7
Hematocrit	10	3	<1	<1	13	5	<1	5
Platelets	1	2	6	5	2	<1	3	<1
<b>Chemistry</b>								
BUN	0	0	2	3	<1	0	3	5
Creatinine	<1	<1	<1	<1	0	0	<1	<1
Bicarbonate	4	4	<1	0	3	4	<1	0
Chloride	0	0	3	2	0	<1	3	3
Potassium	<1	<1	1	2	1	1	<1	<1
Sodium	<1	<1	2	1	<1	<1	2	<1
Alkaline Phosphatase	2	<1	2	3	1	2	4	3
ALT	<1	<1	14	14	<1	0	18	19
AST	<1	<1	7	7	<1	<1	12	9
Bilirubin	3	7	5	7	12	14	3	1
GGT	2	<1	6	5	1	<1	9	10
LDH	0	0	5	2	0	<1	3	2
<b>Urinalysis</b>								
	Shift to High /Positive				Shift to High /Positive			
	Natalizumab	Placebo			Natalizumab	Placebo		
Color	<1	0			<1	<1		
Occult Blood	27	29			24	23		
Glucose	2	3			<1	1		
Ketones	2	2			3	2		
pH	<1	0			<1	<1		
Protein	6	4			4	4		
Specific	3	3			4	4		

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The applicant provided laboratory data for approximately 300 subjects in the Study 1801 placebo group, for approximately 600 subjects in the Study 1801 natalizumab group, and for approximately 560 subjects in each Study 1802 treatment group. The exact number of subjects with data from each test varies slightly for the different laboratory tests, but the approximations given above are within 10% of the exact number for all laboratory studies presented in Table 26.

The increases in total WBC and in total lymphocytes are sufficient to be elevated outside of the normal range in 38% of subjects in Study 1801, the most reliable data to assess the safety of natalizumab alone. The increases in monocytes, basophils, and eosinophils were more modest, affecting 6%, 5%, and 13% of natalizumab-treated subjects in Study 1801, and similar percentages in Study 1802 (Table 26).

Natalizumab was associated with an increased risk of developing a decreased hematocrit, decreased hemoglobin, and especially reduced RBCs. There was no consistent effect on platelet count.

Natalizumab may be associated with a slightly increased risk of an elevation in serum sodium (2% of subjects, versus  $\leq 1\%$  in controls). Natalizumab does not appear to be associated with any other disturbance of serum electrolytes, BUN, or creatinine.

In this analysis, natalizumab alone does not appear to increase the risk of elevation of liver function tests to outside of the normal range. However, when natalizumab was combined with Avonex<sup>®</sup> in Study 1802, natalizumab administration appeared to slightly increase the risk of an elevation in selected liver function studies (aspartate transaminase and bilirubin), compared to Avonex<sup>®</sup> plus placebo.

Compared to placebo, natalizumab was associated with an increase in the incidence of proteinuria in Study 1801; however, this was not observed in Study 1802. No other changes in urinary measures were apparent.

#### 7.1.7.3.3 Marked Outliers and Dropouts for Laboratory Abnormalities

<b>Table 27: Elevations of Liver Function Tests</b>				
	Study 1801		Study 1802	
	Natalizumab	Placebo	Natalizumab + Avonex <sup>®</sup>	Placebo + Avonex <sup>®</sup>
Resulted in dropout from study	0	1	1	0
Resulted in discontinuation of study agent (but not study participation)	0	0	0	1
Serious adverse event	1	1	1	2



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No other routine laboratory measure was associated with a discontinuation of study agent administration and/or study participation. However, one natalizumab group subject in Study 1802 discontinued study agent administration due to an elevation in pancreatic enzymes.

#### 7.1.7.4 Additional Analyses and Explorations

In combined data from all placebo-controlled MS studies, 77 (5%) of 1617 subjects who received natalizumab developed abnormal levels of nucleated red blood cells, in contrast to an elevation of nucleated red blood cells in only 1 of 1135 subjects who received placebo. A similar pattern was seen in the placebo-controlled studies in Crohn's disease.

The sponsor notes that the  $\alpha 4$  integrin,  $\alpha 4\beta 1$ , is involved in the retention of hematopoietic progenitor cells in the bone marrow (see Papayannopoulou, 1993, and Papayannopoulou, 2001, in References). Maturing RBCs express both  $\beta 1$  and  $\beta 2$  integrins which are involved in anchoring the RBC in the marrow. The binding of natalizumab to these maturing RBCs or nucleated RBCs (nRBCs) could enhance their exit from the marrow.

One subject in Study 221 had nRBCs of 13% (relative to 100 WBCs counted/high powered field) following a single dose of natalizumab. The hemoglobin remained stable. In the remaining subjects, nRBCs were detected usually on a single occasion, ranged between 1-4% and were transient. Only 6 of 77 subjects (8%) with detectable nRBCs at any timepoint had hemoglobin levels that dipped below the lower limit of normal. One subject was anemic at baseline with a low MCV, consistent with an iron deficiency type anemia, and remained anemic throughout the study, with hemoglobin ranging from 9.1 – 9.7 g/dL. Another subject was also anemic at baseline with a low MCV, but by Week 24 when nRBCs were noted, the hemoglobin had corrected to 11.3 g/dL. A third subject had nRBCs at Week 48, with a hemoglobin of 10.9 g/dL, which corrected to 11.4 g/dL by Week 60. In the remaining 3 subjects with nRBCs and a low hemoglobin, the finding of low hemoglobin occurred only once. Thus, the appearance of elevated levels of nucleated RBCs is clearly associated with natalizumab, but is of unclear clinical significance.

#### 7.1.7.5 Special Assessments

Several available treatments for MS (all three  $\beta$ -interferons and glatiramer acetate) have been associated with a risk of hepatotoxicity. The data provided in this submission suggests that natalizumab, when administered in combination with a  $\beta$ -interferon, may minimally increase the risk of hepatotoxicity, compared to the risk with the  $\beta$ -interferon alone, as evidenced by the increased frequency of elevated liver function tests reported as adverse events (Table 23) and the shifts in liver function tests noted in Study 1802 (Table 26). This issue will warrant consideration by physicians who plan to co-administer natalizumab and one of these other MS therapies, or any known hepatotoxic agent. This issue will also warrant careful review when final study reports for Studies 1801 and 1802 become available.

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#### 7.1.8 Vital Signs

##### 7.1.8.1 Overview of Vital Signs Testing in the Development Program

For reasons discussed previously (see Section 7.1, Methods and Findings), this review focuses on measurements of vital signs (temperature, pulse, systolic blood pressure, and diastolic blood pressure) in Studies 1801 and 1802, but also considers data from all placebo-controlled MS studies. The two Phase 3 MS studies included measurements of vital signs at all study drug administration visits (every four weeks through Week 116; see Section 6.1.3.1.4, Study 1801 – Study Procedures) within 1 hour prior to infusion of study drug and within 1 hour post-infusion. Subjects were required to sit quietly for 5 minutes prior to assessment of pulse and blood pressure. In addition, Studies 1801 and 1802 included physical examinations, including measurements of vital signs, at Screening, at Weeks 52, 104, and 120, and at premature study withdrawal visits.

##### 7.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

This review focuses on Studies 1801 and 1802, which provide the only substantial database on natalizumab exposure for at least 12 months. For further discussion of the selection of these two studies for analysis, see Section 7.1, Methods and Findings). The analysis of the effect of natalizumab on vital signs focuses on shifts from normal to abnormal.

##### 7.1.8.3 Standard Analyses and Explorations of Vital Signs Data

###### 7.1.8.3.1 Analyses Focused on Outliers or Shifts From Normal to Abnormal

For the placebo-controlled studies (including Studies 1801 and 1802), vital sign abnormalities were defined as outlined in Table 28.

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<b>Table 28: Vital Sign Abnormalities: Definitions</b>		
<b>Vital Sign</b>	<b>Protocol Criteria</b>	<b>Post-hoc Criteria<sup>1</sup></b>
Temperature	>38 °C and an increase from pre-dosing of at least 1 °C	Same as Protocol Criteria
Pulse	>120 beats per minute and an increase from pre-dosing of more than 20 beats per minute, or <50 beats per minute and a decrease from pre-dosing of more than 20 beats per minute	>120 beats per minute and an increase from pre-dosing of more than 10 beats per minute, or <50 beats per minute and a decrease from pre-dosing of more than 10 beats per minute
Systolic Blood Pressure	>180 mmHg and an increase from pre-dosing of more than 40 mmHg, or <90 mmHg and a decrease from pre-dosing of more than 30 mmHg	>180 mmHg and an increase from pre-dosing of more than 10 mmHg, or <90 mmHg and a decrease from pre-dosing of more than 10 mmHg
Diastolic Blood Pressure	>105 mmHg and an increase from pre-dosing of more than 30 mmHg, or <50 mmHg and a decrease from pre-dosing of more than 20 mmHg	>105 mmHg and an increase from pre-dosing of more than 10 mmHg, or <50 mmHg and a decrease from pre-dosing of more than 10 mmHg

<sup>1</sup> Post-hoc criteria were requested by CDER as a sensitivity analysis.

#### 7.1.8.3.1.1 Acute (Post-Infusion) Changes in Vitals Signs

Table 29 summarizes the incidence of vital sign abnormalities observed within an hour post-infusion. Table 29 illustrates that, using the more stringent sensitivity criteria (Table 28, right column), there were no trends apparent to suggest hemodynamically important changes.

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**Table 29: Incidence of Post-Infusion Vital Sign Abnormalities: All MS Studies**

Vital Sign	Protocol Criteria	All MS Studies <sup>1</sup>	
		Natalizumab	Placebo
Temperature	>38 °C and an increase from pre-dosing of at least 1 °C	11/1442 (0.8%)	9/1030 (0.9%)
Pulse	>120 beats per minute and an increase from pre-dosing of more than 20 beats per minute,	1/1615 (0.1%)	3/1135 (0.3%)
	or <50 beats per minute and a decrease from pre-dosing of more than 20 beats per minute	11/1615 (0.7%)	6/1135 (0.5%)
Systolic Blood Pressure	>180 mmHg and an increase from pre-dosing of more than 40 mmHg,	0/1615 (0%)	1/1135 (0.1%)
	or <90 mmHg and a decrease from pre-dosing of more than 30 mmHg	6/1615 (0.4%)	9/1135 (0.8%)
Diastolic Blood Pressure	>105 mmHg and an increase from pre-dosing of more than 30 mmHg,	8/1615 (0.5%)	7/1135 (0.6%)
	or <50 mmHg and a decrease from pre-dosing of more than 20 mmHg	26/1615 (1.6%)	15/1135 (1.3%)
Respiration	<10 or >24 per minute	1/142 (0.1%)	0/71 (0%)

<sup>1</sup> Includes all placebo-controlled MS studies, including Studies 200, 201, 202, 221, 231, 1801, 1802, and 1803 (see Section 4.2, Tables of Clinical Studies). Entries are numbers of subjects meeting criterion / number of subjects being evaluated (%) at infusion visits.

Assessed one hour post-infusion, very few subjects in Study 1801 or 1802 exhibited abnormalities of vital signs

#### 7.1.8.3.1.2 Chronic Abnormalities in Vital Signs

Based on the protocol-specified definitions of vital sign abnormalities, very few vital sign readings in Studies 1801 or 1802 were categorized as abnormal. (The protocol-defined definitions were relatively insensitive to change). Results based on the more sensitive post-hoc definitions are shown in Table 30. Though abnormal vital signs are relatively infrequent, there are clear trends (in both studies) towards greater frequencies of abnormally high, rather than abnormally low, blood pressure measurements (i.e., frequency of hypertension >> hypotension). Similar trends are evident in assessments of pulse (tachycardia >> bradycardia). Given that these trends are evident in both the natalizumab- and placebo-treated groups, they do not suggest chronic changes in vital signs related to natalizumab.

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**Table 30: Incidence of Post-Baseline Abnormalities in Vital Signs, Sensitivity Analysis: Studies 1801 and 1802<sup>1</sup>**

Vital Sign	Protocol Criteria	Study 1801		Study 1802	
		Natalizumab	Placebo	Natalizumab + Avonex®	Placebo + Avonex®
<b>Temperature</b>	>38 °C and an increase from pre-dosing of at least 1 °C	1/627 (0.2%)	0/312 (0%)	11/589 (1.9%)	6/582 (1.0%)
<b>Pulse</b>	>120 beats per minute and an increase from pre-dosing of more than 10 beats per minute	1/627 (0.2%)	0/312 (0%)	12/589 (2.0%)	22/582 (3.8%)
	<50 beats per minute and a decrease from pre-dosing of more than 10 beats per minute	1/627 (0.2%)	2/312 (0.6%)	2/589 (0.3%)	4/582 (0.7%)
<b>Systolic BP</b>	>130 mmHg and an increase from pre-dosing of more than 10 mmHg	3/627 (0.5%)	28/312 (9.0%)	42/589 (7.1%)	37/582 (6.4%)
	<90 mmHg and a decrease from pre-dosing of more than 10 mmHg	1/627 (0.2%)	3/312 (1.0%)	4/589 (0.7%)	1/582 (0.2%)
<b>Diastolic BP</b>	>100 mmHg and an increase from pre-dosing of more than 10 mmHg	3/627 (0.5%)	17/312 (5.4%)	28/589 (4.8%)	26/582 (4.5%)
	<50 mmHg and a decrease from pre-dosing of more than 10 mmHg	7/627 (1.1%)	9/312 (2.9%)	13/589 (2.2%)	13/582 (2.2%)

<sup>1</sup> Based on assessments of vital signs during routine visits at Weeks 52, 104, 120, and at premature withdrawal visits. These values do not include abnormalities recorded immediately post-infusion (see Table 29). Number evaluated is the number of subjects who had a baseline measurement and at least one post-baseline measurement of that vital sign. Numbers in parentheses are percentages based on the number of subjects evaluated.

#### 7.1.8.3.2 Marked Outliers and Dropouts for Vital Sign Abnormalities

In Study 1801, no vital sign abnormality was designated as a serious adverse event, and no vital sign abnormality was the primary reason for discontinuing study medication or dropping out of the study.

In Study 1802, one subject in the placebo plus Avonex® group developed a hypertensive crisis which was classified as a serious adverse event. However, no subject in the natalizumab plus Avonex® group had a vital sign abnormality that was classified as a serious adverse event. No vital sign abnormality was the primary reason for dropping out of the study. In the natalizumab

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plus Avonex<sup>®</sup> group, three subjects discontinued study medication due to tachycardia, and one subject discontinued study medication due to hypotension. In the placebo plus Avonex<sup>®</sup> group, one subject discontinued study medication due to hypertensive crisis, and one subject discontinued study medication due to tachycardia.

#### 7.1.8.4 Additional Analyses and Explorations

No additional analyses and explorations are indicated. Overall, natalizumab-induced changes in vital signs, either during the two hours after the initiation of natalizumab administration or during routine monitoring as part of scheduled physical examinations, were uncommon and/or mild.

#### 7.1.9 Electrocardiograms (ECGs)

##### 7.1.9.1 Overview of ECG Testing in the Development Program, Including Brief Review of Preclinical Results

In Elan Study #723-013-98, 32 cynomolgous monkeys received intravenous natalizumab, including 10 monkeys that received the highest dose of 60 mg/kg, every week for up to 26 weeks. In Study #1164-87, 40 rhesus monkeys received natalizumab, including 20 monkeys that received the highest dose of 60 mg/kg, every week for 4 weeks. In Elan Study #309-011-00, 22 juvenile cynomolgus monkeys received intravenous natalizumab, including 10 monkeys that received the highest dose of 60 mg/kg, every week for up to 6 months. The monkeys in all three studies were monitored with ECGs, which did not reveal any treatment-related abnormalities. Also, no cardiac toxicity was noted on necropsy. For additional information regarding the preclinical assessments of cardiotoxicity, see the Non-clinical Toxicology review by Dr. Barbara Wilcox.

The clinical development program included electrocardiographic monitoring, but did not include systematic assessment for prolongation of the QT interval. The two Phase 3 MS studies which form the basis for this application did not include routine ECGs as part of the monitoring of study subjects. ECG data were evaluated in the Phase 1 and 2 studies..

Of note, prolongation of the QT interval, torsades de pointes, and sudden death have not been associated with other monoclonal antibodies.

##### 7.1.9.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

In Study 101, 35 normal volunteers were randomized to receive a single administration of natalizumab (26 subjects) or placebo (9 subjects). Natalizumab doses ranged from 0.03 mg/kg to 3 mg/kg. The study included serial electrocardiograms through Day 92 post-administration of study agent. The applicant reports that there were no clinically significant ECG abnormalities.



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In Study 200, 28 subjects were randomized to receive a single IV dose of either natalizumab (21 subjects) or placebo (7 subjects). This was a dose-escalation study with weight-adjusted dosing. ECG monitoring was included in the study; no ECG abnormalities were noted.

Study 224 also included routine ECG monitoring for 38 subjects who received either 3 mg/kg or 6 mg/kg every 4 weeks for at least 3 months. The applicant reports that analysis of ECG data did not raise any safety concerns.

Study 202 included routine ECG monitoring for subjects who received a single administration of either 1 mg/kg natalizumab (57 subjects), 3 mg/kg natalizumab (60 subjects), or placebo (63 subjects). The applicant reports that there were no clinically important differences among the groups in ECG parameters.

Study 231 administered natalizumab (3 mg/kg, 6 mg/kg, or placebo) to 213 MS subjects every 4 weeks for 20 weeks. The study included routine monitoring of ECGs. The applicant reports that there were no clinically significant differences between the groups in ECG parameters.

In Study 1806, a single IV administration of natalizumab, either one of two formulations, was administered to 86 normal volunteers. There were no clinically significant abnormalities in ECG results following dosing with either of two formulations of natalizumab.

#### 7.1.9.3 Standard Analyses and Explorations of ECG Data

The electrocardiogram database was not sufficient to support meaningful exploratory analyses. In placebo-controlled MS studies, there were four subjects with cardiac events (including two myocardial infarctions and one cardiomyopathy) in the placebo groups and one subject with a cardiac event (acute myocardial infarction) in the natalizumab groups.

The adverse event profile does not suggest an increased incidence of cardiac events to warrant further studies by the applicant of the effect of natalizumab on ECG parameters.

#### 7.1.9.4 Additional Analyses and Explorations

One 41 year-old woman who received natalizumab in a placebo-controlled MS study developed ST segment depression on an electrocardiogram, which was reported as a serious adverse event of moderate severity. The event occurred after the subject had received 16 infusions in Study 1801, and did not result in discontinuation of the study drug. The significance of this event, in isolation, is uncertain.

#### 7.1.10 Immunogenicity

Treatment with therapeutic proteins such as natalizumab can lead to formation of antibodies directed against the product. The formation of antibodies may be either transient or persistent. In Studies 1801 and 1802, sera were obtained every 12 weeks for determination of anti-natalizumab antibodies. A screening ELISA assay was used, followed by a



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assay in those who were screening antibody-positive and had no detectable natalizumab in the serum. Because of the high correlation between the screening ELISA results and the

assay, only the ELISA results are presented here. Antibody positivity was defined as a serum titer  $\geq 0.5$   $\mu\text{g/mL}$ . For purposes of the 1-year analyses of Studies 1801 and 1802 presented in this review, antibody responses were characterized as persistently positive (positive on two or more occasions separated by at least 42 days or at the last time point tested), transiently positive (positive titer not fulfilling the criteria for persistently positive), or antibody negative (no detectable antibody at any timepoint). However, the assays used in these studies were unable to detect low to moderate levels of antibodies to natalizumab. One problem with the assay is that the presence of natalizumab was found to interfere with detection of antibodies to natalizumab. For a more detailed discussion of the limitations of the assay methods, please see the Chemistry, Manufacturing, and Controls (CMC) review by Drs. Elena Gubina, Joseph Kutza, and Lei Zhang.

#### 7.1.10.1 Immunogenicity Results

Of 1216 natalizumab-treated subjects evaluated in the combined Phase 3 MS studies, 10% (126) had a positive anti-natalizumab antibody titer at least once, and 6% (75) had persistently positive titers (Table 31). Of 863 natalizumab-treated subjects in the integrated CD studies (CD301, CD303, CD306, and CD351), 10% (87) had a positive anti-natalizumab antibody titer at least once, and 8% (70) had persistently positive titers.

**Table 31: Studies 1801 and 1802: Antibody Status (Applicant's Analysis)**

	Study 1801	Study 1802
	Natalizumab	Natalizumab + Avonex <sup>®</sup>
Subjects randomized	627	589
Subjects evaluated <sup>1</sup>	625 (99.7%)	585 (99.3%)
Antibody negative <sup>2</sup>	568 (91%)	516 (88%)
Any positive antibody	57 (9%)	69 (12%)
Transient antibody-positive <sup>3</sup>	20 (3%)	31 (5%)
Persistent antibody-positive <sup>4</sup>	37 (6%)	38 (6%)
Time to antibody-positive = 0-13 weeks <sup>5</sup>	47 (82%)	66 (96%)
Time to antibody-positive = 13 – 26 weeks <sup>5</sup>	7 (12%)	3 (4%)
Time to antibody-positive = > 26 weeks <sup>5</sup>	3 (5%)	0 (0%)
Anti-Avonex antibody at Week 24	-	18 (3%) <sup>6</sup>

<sup>1</sup> Subjects with one or more post-baseline screening antibody result.

<sup>2</sup> Defined as  $< 0.5$   $\mu\text{g/mL}$  at all post-baseline visits.

<sup>3</sup> Defined as  $\geq 0.5$   $\mu\text{g/mL}$  at only one post-baseline visit prior to the last visit.

<sup>4</sup> Defined as  $\geq 0.5$   $\mu\text{g/mL}$  at two or more post-baseline visits  $\geq 42$  days apart or  $\geq 0.5$   $\mu\text{g/mL}$  at the last post-baseline visit.

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<sup>5</sup> Percentage calculated as the number with the first positive result in the specified time period / number with one or more positive ( $\geq 0.5 \mu\text{g/mL}$ ) post-baseline results.

<sup>6</sup> Compared to 10 (2%) in the Avonex<sup>®</sup> + placebo group

The time to antibody formation ranged from 6 to 60 weeks after the initial administration of natalizumab; however, 82 – 96% of subjects who developed detectable antibodies did so within the first 3 months.

The rate of antibody formation was similar in the two Phase 3 studies (Table 31), indicating that Avonex<sup>®</sup> did not have a substantial effect on the frequency of anti-natalizumab antibody positivity.

#### 7.1.10.2 Antibody Status and Infusion Reactions

Table 32 enumerates the incidence of adverse events, including acute hypersensitivity reactions, according to antibody status, for subjects in Studies 1801 and 1802.

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<b>Table 32: Infusion Reactions<sup>1</sup> by Antibody Status, Studies 1801 and 1802 Combined</b>			
	Natalizumab Antibody Status		
	Negative	Transient positive	Persistent positive
N (%)	1084 (100)	51 (100)	75 (100)
Any infusion reaction	192 (18)	15 (29)	58 (77)
Rigors	1 (<1)	0 (0)	15 (20)
Urticaria	5 (<1)	1 (2)	11 (15)
Hypersensitivity	0 (0)	0 (0)	7 (9)
Pruritus	6 (1)	2 (4)	5 (7)
Anaphylactic / Anaphylactoid	0 (0)	1 (2)	4 (5)
Dyspnea	0 (0)	0 (0)	4 (5)
Tremor	0 (0)	0 (0)	4 (5)
Tachycardia	1 (<1)	0 (0)	4 (5)
Feeling cold	0 (0)	0 (0)	4 (5)
Nausea and/or vomiting	15 (1.4)	0 (0)	13 (17.3)
Headache	36 (3)	1 (2)	12 (16)
Flushing	6 (1)	0 (0)	7 (9)
Dizziness	29 (3)	0 (0)	5 (7)
Psychiatric disorders (including nervousness, anxiety, restlessness, disorientation, and depression)	2 (<1)	1 (2)	3 (4)
Hypotension	3 (<1)	0 (0)	3 (4)
Pyrexia	6 (1)	0 (0)	3 (4)

<sup>1</sup> By definition, "infusion reactions" were defined as any event that occurred within 2 hours of the initiation of study agent infusion. Includes all events that occurred in at least 3 subjects who were persistently antibody-positive. From sponsor's analysis of events.

Antibody formation is associated with an increase in the rate of infusion reactions. This is particularly true for infusion reactions that are generally considered to have an immune basis (e.g., urticaria, rigors, and anaphylaxis). Overall, 77% of subjects who were persistently antibody positive reported some type of infusion reaction. Conversely, subjects who have these typical immune-mediated infusion reactions are very likely to be persistently antibody-positive.

The protocols for Studies 1801 and 1802 specified that subjects who developed hypersensitivity reactions would discontinue study medication.

Table 33 summarizes the incidence of common adverse events in Studies 1801 and 1802 combined, grouped by natalizumab antibody status (as defined above). Events are listed in descending frequency for persistently positive subjects.

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**Table 33: Common Adverse Events by Antibody Status, Studies 1801 and 1802<sup>1</sup> Combined**

	Natalizumab Antibody Status		
	Negative	Transient Positive	Persistent Positive
<b>N (%)</b>	1084 (100)	51 (100)	75 (100)
Any adverse event	1037 (96)	49 (96)	72 (96)
Fatigue	274 (25)	14 (27)	20 (27)
Nausea	140 (13)	6 (12)	18 (24)
Rigors	22 (2)	1 (2)	17 (23)
Back pain	179 (17)	5 (10)	16 (21)
Arthralgia	179 (17)	9 (18)	14 (19)
Influenza	164 (15)	9 (18)	14 (19)
Urticaria	15 (1)	2 (4)	13 (17)
Myalgia	68 (6)	0 (0)	13 (17)
Diarrhea	128 (12)	4 (8)	12 (16)
Influenza-like illness	120 (11)	10 (20)	11 (15)
Vomiting	61 (6)	2 (4)	10 (13)
Anxiety	77 (7)	5 (10)	9 (12)
Depression	174 (16)	8 (16)	8 (11)
Cough	79 (7)	6 (12)	8 (11)
Muscle spasms	66 (6)	3 (6)	8 (11)
Fall	64 (6)	1 (2)	8 (11)
Flushing	23 (2)	0 (0)	8 (11)
Pruritus	40 (4)	4 (8)	7 (9)
Gastroenteritis, viral	63 (6)	2 (4)	7 (9)
Muscle cramp	55 (5)	0 (0)	7 (9)
Musculoskeletal stiffness	50 (5)	3 (6)	6 (8)
Pharyngolaryngeal pain	56 (5)	1 (2)	6 (8)
Abdominal pain, upper	49 (5)	0 (0)	6 (8)
Peripheral edema	33 (3)	4 (8)	5 (7)
Hypertension	21 (2)	1 (2)	5 (7)
Dyspnea	18 (2)	1 (2)	5 (7)
Tremor	32 (3)	0 (0)	5 (7)
Tachycardia	12 (1)	0 (0)	5 (7)
Sinus congestion	30 (3)	1 (2)	4 (5)
Feeling cold	8 (1)	0 (0)	4 (5)
Feeling hot	11 (1)	3 (6)	3 (4)
Seasonal allergy	35 (3)	2 (4)	3 (4)
Erythema	19 (2)	0 (0)	3 (4)
Abdominal distension	13 (1)	0 (0)	3 (4)
Hypotension	12 (1)	0 (0)	3 (4)
Irritability	11 (1)	0 (0)	3 (4)
Chest discomfort	5 (<1)	0 (0)	3 (4)
Throat irritation	6 (1)	0 (0)	2 (3)

<sup>1</sup> Includes all events, except neurologic events typically associated with multiple sclerosis, which occurred in at least 2 (3%) of subjects who were persistently antibody-positive and which occurred with an incidence at least 2% higher in persistently antibody-positive subjects compared to antibody negative subjects; table also includes some events of interest (e.g., depression) which do not meet these criteria, but are of particular interest because of either the study population or the mechanism of action of natalizumab; above data are derived from analyses by the applicant.

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Events that are generally associated with allergic reactions (e.g., rigors and urticaria) are much more common in subjects who are persistently antibody-positive than in subjects who are antibody negative. Antibody status does not have a clear correlation with the rate of infection. Subjects who are antibody-positive have slightly lower rates of depression. However, as for most of the types of events in the above table, the number of events is low, making interpretation difficult.

#### 7.1.10.3 Antibody Status and Efficacy Outcomes

The relationships between relapse rate, MRI findings, and antibody status are shown in Table 34, based on 1-year data provided by the applicant. In this analysis, one fewer subject is characterized as transiently antibody-positive, and one fewer subject is classed as persistently antibody-positive, relative to Table 31, which is based on data submitted as part of the 120-day Safety Update (Amendment 12 to the original application).

<b>Table 34: Primary and Secondary Outcome Measures by Antibody (Ab) Status</b>								
	Study 1801				Study 1802			
	Placebo	Natalizumab			Placebo + Avonex <sup>®</sup>	Natalizumab + Avonex		
		Ab -	Transient antibody +	Persistent antibody +		Ab -	Transient antibody +	Persistent antibody +
N	315	569	19	37	582	514	31	37
Relapse rate	0.698	0.223	0.276	0.462	0.746	0.333	0.420	0.536
Proportion of relapse-free subjects; N (%)	166 (53)	443 (78)	14 (74)	17 (46)	265 (46)	351 (68)	16 (52)	23 (62)
Number of gadolinium- enhancing lesions (mean)	1.2	0.1	0.0	0.6	0.8	0.1	0.1	0.7
Number of new or newly enlarging T2 lesions (mean)	6.1	1.1	0.7	3.3	2.1	0.4	0.7	1.8

For each of the primary and secondary outcome measures, subjects who are antibody-positive appear to have outcomes intermediate between the relatively favorable outcomes in subjects who are antibody negative and the relatively unfavorable outcomes in subjects who received placebo. Subjects with transient antibody positivity tend to have outcomes intermediate between subjects with persistent antibody positivity and subjects who are consistently antibody negative. This indirect correlation between antibody positivity and improvement in outcome is generally consistent across the above outcome measures in both studies.

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The applicant provided additional analyses to demonstrate the relationship between antibody status and relapse rate. For subjects who became persistently antibody-positive in Study 1801, the annualized relapse rate following the first appearance of antibody was 0.75, similar to the relapse rate of 0.74 in subjects who received placebo. For subjects who became persistently antibody-positive in Study 1802, the annualized relapse rate following the first appearance of antibody was 0.60, intermediate between the relapse rate of 0.78 in subjects who received placebo and the rate of 0.35 in subjects who remained antibody negative.

Thus, the development of antibodies, particularly persistently-positive antibodies, is strongly associated with a decrease, if not a complete loss, of efficacy of natalizumab. The development of transiently-positive antibodies appears to be associated with a smaller decrease in efficacy than is seen with persistently-positive antibodies. Although this data is sufficient to establish the importance of antibody formation with regard to natalizumab activity, the data are incomplete. Results from long-term exposure of at least two years will be necessary, along with development of a more sensitive assay to detect antibodies, to permit a more complete assessment of the importance of immunogenicity with use of natalizumab.

#### 7.1.11 Human Carcinogenicity

Immunosuppressant drugs such as azathioprine and cyclosporine have been associated with an increased risk of malignancy. By interfering with lymphocyte trafficking, natalizumab has the theoretical potential to impair immune surveillance, thereby increasing the incidence of malignancy. In placebo-controlled MS studies, 7 natalizumab-treated subjects (0.4%) and 10 placebo-group subjects (0.9%) developed malignancies. The rate of malignancy in natalizumab-treated subjects was 0.32 per 100 person years compared to 0.65 per 100 person years in the placebo group. The malignancies are listed in Table 35.

<b>Table 35: Malignancy Incidence in MS Studies*</b>		
	Natalizumab	Placebo
Number of subjects (N)	1617	1135
Subjects with a malignancy	7	10
Basal cell carcinoma	3	3
Breast cancer	3	2
Malignant melanoma	1	2
Malignant pleural effusion	0	1
Secretory adenoma of pituitary	0	1
Squamous cell carcinoma of the skin	0	1

\* Includes all placebo-controlled MS studies, including Studies 200, 201, 202, 221, 231, 1801, 1802, and 1803 (see Section 4.2, Tables of Clinical Studies).

For the relatively limited duration of clinical exposure in the natalizumab MS development program, natalizumab is not associated with an increase in malignancy. However, the database



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(see Section 7.1, Methods and Findings) does not include sufficient numbers of subjects with long-term exposure that would be needed to detect a relatively uncommon event such as malignancy. This issue will need to be reassessed when the applicant submits the final study reports for Studies 1801 and 1802.

#### 7.1.12 Special Safety Studies

No special safety studies were included in the development of this product (see Section 4.2, Tables of Clinical Studies).

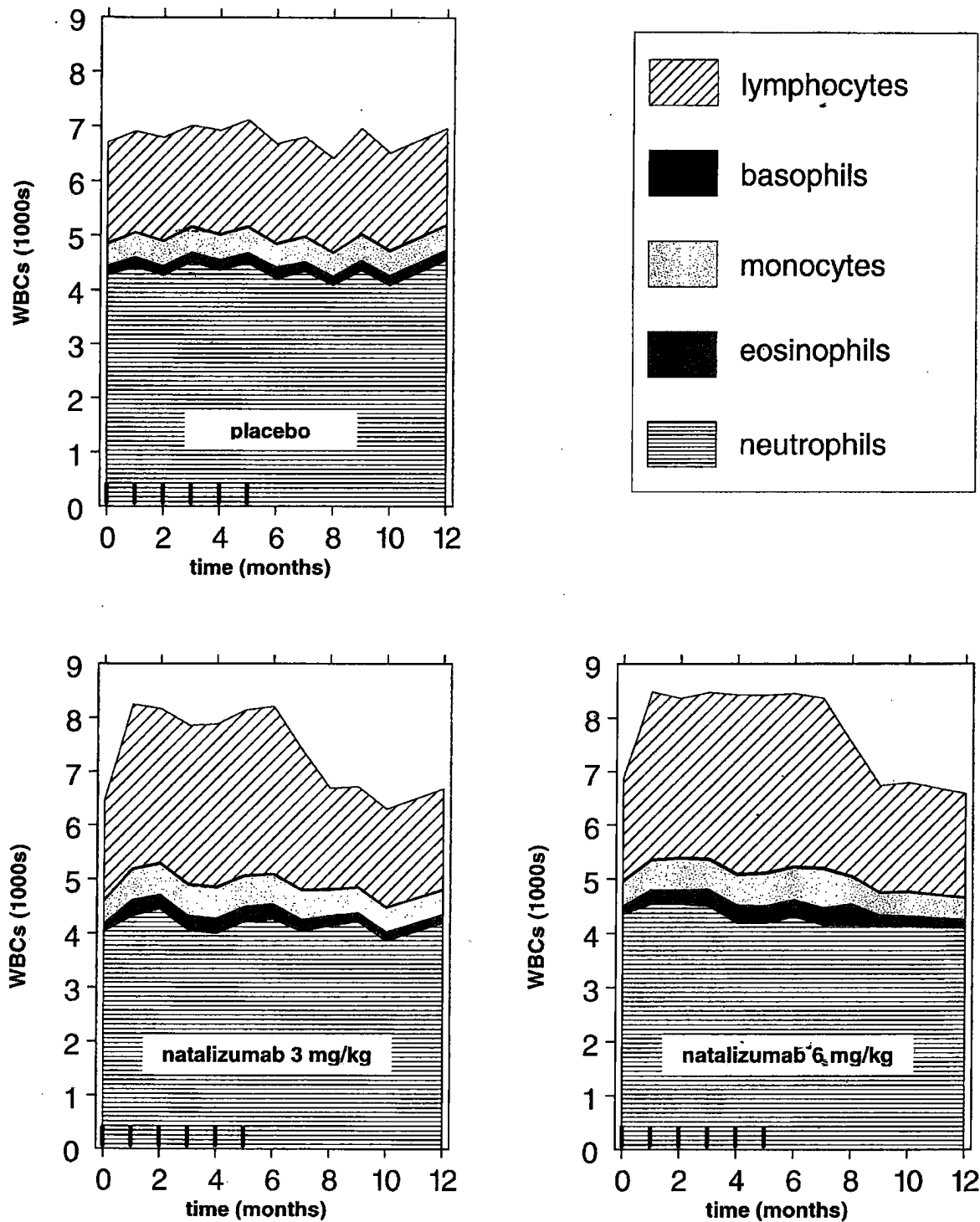
#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Study 231 (see Section 10.1.1, Study 231) is the only placebo-controlled MS study that included administration of natalizumab for at least 3 months with follow-up off medication for at least 3 months. Considering the half-life of natalizumab of approximately 10 days (see Section 5.1, Pharmacokinetics) and the pharmacodynamic effects which can last for several months, follow-up for periods less than 2-3 months may be insufficient to assess drug withdrawal. In Study 231, subjects received 6 infusions of natalizumab, either 3 mg/kg or 6 mg/kg, or placebo over 20 weeks. During the 6-month treatment period, relapses occurred in 38% (27/71) of the subjects who received placebo and in 19% (13/68 in 3 mg/kg group; 14/74 in 6 mg/kg group) of the subjects who received natalizumab. During the follow-up period, relapses occurred in 35% (24/69) of the placebo-treated subjects and in 33% (44/134) of the natalizumab-treated subjects. During the 6-month follow-up, the need for steroids to treat the relapses was similar between the groups (20% natalizumab-treated versus 19% placebo-treated). This study, which provides the best assessment to date of the effect of drug withdrawal in MS subjects, shows no evidence of a rebound increase in relapses following drug withdrawal. Although Study 231 used weight-adjusted dosing, the dosing is similar to the proposed recommended fixed dose of 300 mg.

Study 231 (see Section 9.6.1, Study 231) also provides data on laboratory measures following study agent discontinuation. Increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells (Table 25; Table 26) are reversible, returning to baseline levels usually within 16 weeks after the last dose. However, Study 231 provides evidence that there may be a small rebound decrease (mean decrease  $\leq 5\%$  compared to baseline) in some of these laboratory measures, particularly the total WBC and the total lymphocyte count. Although the magnitude of this rebound was small, a few subjects ( $\leq 4$  subjects [6%] in each natalizumab group) had a shift in a specific measure (usually total WBC or total lymphocytes) from normal to low, comparing the values 4 – 7 months following natalizumab discontinuation to the baseline value. The rebound was more prominent in the 6 mg/kg group than in the 3 mg/kg group, and appears to have plateaued by 7 months following the last dose of natalizumab.

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**Figure 1: Time Course in Changes in Leukocytes, Study 231**



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Figure 1 shows the changes in white blood cell counts that occurred with administration and discontinuation of natalizumab in Study 231. Study agent, either natalizumab (bottom panels) or placebo (top panel), was administered every four weeks for a total of six doses, designated by the short vertical hash marks extending up from the x-axis at Months 0-5 on each of the three graphs. In the placebo group, the leukocyte counts show only minor, inconsistent fluctuations. In the two natalizumab groups, the neutrophil counts remain relatively stable during the period of natalizumab administration. However, other leukocyte subsets (particularly the lymphocytes, eosinophils, and monocytes) expand rapidly following the first administration of natalizumab and remain elevated until approximately 2 – 4 months following the last dose of natalizumab. In the 6 mg/kg natalizumab group, the mean total WBC and the total lymphocyte count trend slightly lower at 12 months than at baseline, presenting weak evidence of a possible rebound effect.

Considering the dose-related frequency of this possible rebound, a rebound decrease in leukocytes is most likely to occur in patients with relatively low weight who receive the proposed fixed dose of natalizumab. In addition, the subjects in Study 231 discontinued natalizumab after receiving 6 doses over 20 weeks. Any rebound may be larger in magnitude, and either earlier or later in occurrence, in patients who take natalizumab for longer periods of time prior to discontinuing the drug. The available data are insufficient to confirm the existence of a rebound decrease in these hematology measurements. Additional long-term experience in patients who discontinue taking the 300 mg natalizumab dose will be necessary to confirm the existence of a rebound and to assess the clinical meaningfulness of any possible rebound. However, the data from Study 231 suggests that such rebounds, if they occur, are unlikely to be clinically meaningful.

The two placebo-controlled Phase 3 studies, Studies 1801 and 1802, offer an open-label follow-up study for study completers. Therefore, very few subjects who tolerate natalizumab and do well clinically while on these two studies are expected to actually withdraw from natalizumab. Subjects who discontinue study drug in Studies 1801 and 1802, either due to inability to tolerate the drug or due to adverse events, constitute a select population that will provide only limited information regarding the effect of drug withdrawal.

The potential for abuse has not been specifically studied. However, natalizumab has no known effects likely to present a high potential for abuse.

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#### 7.1.14 Human Reproduction and Pregnancy Data

Table 36 summarizes the pregnancy outcomes from all MS and CD studies of natalizumab (see Section 4.2, Tables of Clinical Studies).

<b>Table 36: Pregnancy Outcomes</b>				
Number (%)	Multiple Sclerosis		Crohn's Disease	
	Natalizumab	Placebo	Natalizumab	Placebo
Total number of pregnancies	22 (100)	10 (100)	19 (100)	2 (100)
Spontaneous abortions	2 (9)	3 (30)	4 (21)	1 (50)
Elective abortions	9 (41)	3 (30)	4 (21)	0
Live birth	4 (18)	2 (20)	8 (42)	1 (50)
Pregnancy ongoing	7 (32)	2 (20)	3 (16)	0

There were a total of 12 live births with exposure to natalizumab. Of these 12 children, one was born prematurely at week 30 and was healthy. No congenital abnormalities or teratogenic effects have been detected. The rate of spontaneous abortion, including early pregnancy losses (miscarriages), does not exceed the expected rate within the general population of 12-22% (Garcia-Enguidanos et al, 2002). Pending additional data regarding the effects of natalizumab on pregnancy, the applicant recommends that women of childbearing potential use birth control while receiving natalizumab.

#### 7.1.15 Assessment of Effect on Growth

Natalizumab has not been studied in the pediatric population, except in one 5 year-old girl (see Section 4.2, Tables of Clinical Studies, and Section 7.1.1, Deaths). Due to the low incidence of MS in childhood, the applicant does not currently plan to do pediatric studies of natalizumab (see Section 2.5.3, Pediatric Waiver).

#### 7.1.16 Overdose Experience

The highest dose used in the clinical development programs was 6 mg/kg when administered to the heaviest patients (see Section 4.2, Tables of Clinical Studies). No differences in safety profiles were seen between this 6 mg/kg dose and 3 mg/kg in Phase 2 studies. For most patients (i.e., patients weighing between 50 and 100 kg), the proposed recommended natalizumab dose of 300 mg is between 6 and 3 mg/kg, respectively.

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#### 7.1.17 Postmarketing Experience

Natalizumab is not approved for use for any indication anywhere in the world. There is no postmarketing experience with natalizumab.

### 7.2 Adequacy of Patient Exposure and Safety Assessments

#### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 1617 multiple sclerosis patients, including 1216 in Studies 1801 and 1802, have been exposed to natalizumab with a median duration of exposure of 20 months. The total exposure to natalizumab in placebo-controlled MS and CD trials (see Section 4.2, Tables of Clinical Studies) is outlined in Table 19 (see Section 7.1, Methods and Findings). This safety review is based primarily on the experience in Studies 1801 and 1802 (see Section 6.1.3, Study Design), which are the only large, placebo-controlled clinical trials that administered the proposed recommended dose of natalizumab to MS subjects for more than 6 months.

##### 7.2.1.1 Study Type and Design/Patient Enumeration

Table 1 and Table 2 (see Section 4.2, Tables of Clinical Studies) describe the overall clinical development of natalizumab for MS and other indications.

##### 7.2.1.2 Demographics

Considering that MS is largely a disease of Caucasians in their 30s and 40s, demographic groups were reasonably represented, with the exception of patients of African ancestry. These subjects constituted only 2% (22/1216) of the Phase 3 database. Part of this limitation stems from the fact that only 11% and 62% of subjects enrolled in Studies 1801 and 1802, respectively, were from U.S. sites. However, nothing about the biology of MS, its typical co-morbidities, or the biologic actions of natalizumab suggest a particular susceptibility of African Americans, and the data are deemed adequate.

Demographics for Studies 1801 and 1802 are summarized in Table 3 (see Section 6.1.4.1, Baseline Characteristics). As noted above (see Section 6.1.3, Study Design), these two studies provide the primary basis for the safety review.

##### 7.2.1.3 Extent of exposure (dose/duration)

Early clinical development of natalizumab exposed subjects to weight-adjusted dosing ranging from 0.03 – 6 mg/kg (see Section 4.2, Tables of Clinical Studies). However, the majority of these trials do not contribute significantly to either the efficacy or safety database. Studies 1801 and 1802 (see Section 6.1.3, Study Design) are the only large, placebo-controlled clinical trials that administered the proposed recommended dose of natalizumab to MS subjects for more than

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6 months. The total exposure to natalizumab in placebo-controlled MS trials is outlined in Table 19 (see Section 7.1, Methods and Findings).

#### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There is no postmarketing experience with natalizumab. The applicant did not submit any secondary source data. This review does not consider any secondary clinical data sources.

#### 7.2.3 Adequacy of Overall Clinical Experience

This application and review rely primarily on Studies 1801 and 1802 for evidence of the safety and efficacy of natalizumab. These two studies provide placebo-controlled experience with natalizumab in 1216 subjects with multiple sclerosis and provide a sufficiently large primary database in this orphan disease (see Section 2, Introduction and Background). The number of subjects in Studies 1801 and 1802 is comparable to, or larger than, the number of subjects evaluated in pivotal clinical trials of currently-approved therapies (Avonex<sup>®</sup>, Betaseron<sup>®</sup>, Copaxone<sup>®</sup>, and Rebif<sup>®</sup>). However, the assessment of safety in this review is based on a median of 20 months of exposure to natalizumab; this duration of exposure is suboptimal, and a more complete assessment of the safety of natalizumab depends on the completion of Studies 1801 and 1802.

#### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Special toxicology studies included immunotoxicology studies, a study in juvenile monkeys, and a study of the interaction of natalizumab and Avonex<sup>®</sup>. Immunotoxicology studies of a humanized antibody are difficult to interpret because humanized proteins are often immunogenic in non-human species. In Study AN1000226, intravenous natalizumab was generally well-tolerated by juvenile cynomolgus monkeys; this study has limited relevance for the MS population.

In Biogen Study #P00002-01-01, the combination of Avonex<sup>®</sup> and natalizumab was generally well-tolerated by rhesus monkeys. For additional information regarding these preclinical toxicology studies, see the Non-clinical Toxicology review of this application by Dr. Barbara Wilcox.

#### 7.2.5 Adequacy of Routine Clinical Testing

The methods for acquisition of laboratory, vital sign, ECG, immunogenicity, and adverse event data in Studies 1801 and 1802 are described in Sections 7.1.7 (Laboratory Findings), 7.1.8 (Vital Signs), 7.1.9 (Electrocardiograms (ECGs)), 7.1.10 (Immunogenicity), and 7.1.5 (Common Adverse Events). These methods were adequate to assess the safety of natalizumab.



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#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

A discussion of the interaction of natalizumab with interferon  $\beta$ -1a (Avonex<sup>®</sup>) and with glatiramer acetate (Copaxone) is available in Section 5, Clinical Pharmacology, and in the Clinical Pharmacology review of this application by Dr. Iftexhar Mahmood.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The anticipated adverse events for natalizumab, a humanized monoclonal antibody that inhibits the migration of white blood cells, include infections, malignancy, and adverse events related to immunogenicity. The applicant's assessment of these events is considered in Sections 7.1.5 (Common Adverse Events), 7.1.10 (Immunogenicity), and 7.1.11, (Human Carcinogenicity).

The sponsor has not adequately studied the following safety issues:

- The effect of natalizumab on pregnancy outcomes (see Section 7.1.14, Human Reproduction and Pregnancy Data), including the postnatal health status of the children. This issue is of great importance, particularly considering that many patients with MS are women with child-bearing potential.
- The effect of natalizumab on neoantigen immunization and on recall antigen responses. As an immunosuppressant, natalizumab may interfere with the ability to generate a beneficial response to a vaccine, such as the influenza or pneumococcal vaccines. For MS patients with advanced disability, such immunizations are currently incorporated into routine care.
- The effect of immunogenicity on the safety of natalizumab. The current assay for antibodies to natalizumab is relatively insensitive, and a more sensitive assay is necessary (see Section 7.1.10, Immunogenicity) to more fully assess the safety of natalizumab.

See Section 9.3.2, Required Phase 4 Commitments.

#### 7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety review is generally very high quality, including two large, multicenter, randomized, double-blind, placebo-controlled, Phase 3 trials (Studies 1801 and 1802). However, this review is based on partial results from these two Phase 3 trials, which are both ongoing.

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### 7.2.9 Additional Submissions, Including Safety Update

The original application was submitted on 5/28/04. The applicant submitted the following amendments with data and analyses relating to the safety of natalizumab:

- Amendment 2 (submitted 7/29/04) contains a final study report for Study 1803 (see Section 9.6.2, Study 1803).
- Amendments 3, 7, 11, 27, 31, 32, 33, 34, and 36 contain safety information (see Section 4.1, Sources of Clinical Data) provided by the applicant in response to CDER information requests.
- Amendment 12 (submitted 9/23/04) contains a 120-day Safety update, which includes Study 1801 safety data through March 1, 2004 and Study 1802 safety data through April 15, 2004 (see Section 7.1, Methods and Findings).

Review of each of these amendments has been incorporated into this review.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Important adverse events that are likely to be treatment-related include infections, hypersensitivity reactions, depression, menstrual disorders, headache, and fatigue (see Section 7.1.5, Common Adverse Events). Very few of these adverse events were either severe or serious adverse events (see also Section 7.1.4, Other Serious Adverse Events).

### 7.3.1 Infections

The incidence of urinary tract infections, gastroenteritis, lower respiratory tract infections, vaginitis, and tonsillitis, was increased in subjects who received natalizumab. These infections were generally routine and did not have a complicated course.

### 7.3.2 Hypersensitivity Reactions

Natalizumab has been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis) at an incidence of <1%. These reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Many of these reactions are associated with antibodies to natalizumab (see Section 7.1.10, Immunogenicity).

### 7.3.3 Elevated Liver Function Tests

Currently available interferon beta therapies for MS are associated with liver function abnormalities (see Section 2.2.1, Immune Modulators Approved for Treatment of MS). The

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potential for natalizumab to cause liver abnormalities raises the possibility of synergistic hepatotoxicity if natalizumab is co-administered with available agents. However, the safety data suggests that natalizumab alone, and in combination with an interferon beta, causes relatively minor, if any, hepatotoxicity (see Sections 7.1.3.1 Overall profile of dropouts, 7.1.2 Other Serious Adverse Events, and 7.1.7 Laboratory Findings).

#### 7.3.4 Depression

Currently available interferon beta therapies for MS may increase the risk of depression. The potential for natalizumab to cause depression raises the possibility of synergistic toxicity if natalizumab is co-administered with a beta-interferon. There were small trends in favor of depression in natalizumab-treated subjects (versus control subjects), both in Study 1801 and Study 1802 (Table 23). The significance of these trends is magnified by the fact that natalizumab-treated subjects experienced fewer relapses than control subjects. Of note, the increase in the incidence of depression associated with natalizumab was not significantly altered by the co-administration of an interferon- $\beta$  (Avonex<sup>®</sup>) (see Section 7.1.5.4, Common adverse event tables).

#### 7.3.5 Menstrual disorders

Natalizumab administration was associated with an increased incidence of menstrual disorders in Studies 1801, 1802, and 1803 (see Section 7.1.5.4, Common adverse event tables, and Table 40). Specific menstrual disorders associated with the use of natalizumab include dysmenorrhea, menstrual irregularities, and amenorrhea.

#### 7.3.6 Other Common Adverse Events

Other common adverse events included headache, fatigue, arthralgia, abdominal discomfort, and syncope. Each of these occurred only slightly more often (absolute increase of 2 - 6%) in the natalizumab groups compared to the placebo groups, and the adverse events were seldom serious (see Section 7.1.5.4, Common adverse event tables, and Section 7.1.4, Other Serious Adverse Events).

Fatigue may be a manifestation of the subject's underlying MS, rather than an effect of natalizumab. The natalizumab group had a higher incidence of fatigue in Study 1801 but a lower incidence of fatigue in Studies 231 (Table 39) and 1802. This lack of reproducibility indicates that the increased incidence of fatigue associated with natalizumab administration in Study 1801 may be a spurious finding. Such comparisons across studies can be informative, but should be viewed with caution.

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## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

#### 7.4.1.1 Pooled Data vs. Individual Study Data

This safety review includes some pooling of MS studies (see Section 7.1.7, Laboratory Findings). However, this review does not pool studies of natalizumab for different indications (i.e., MS and CD). Pooling was also limited to placebo-controlled studies.

#### 7.4.1.2 Combining Data

This review pools studies by simple combination of numerators and denominators and does not employ other pooling procedures.

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.1 Explorations for Dose Dependency for Adverse Findings

Subjects in the two Phase 3 studies received a fixed 300 mg dose of natalizumab. Therefore, exposure to natalizumab on a mg/kg basis was inversely related to subject weight. This provided an opportunity to assess the frequencies of adverse events as a function of subject weight, i.e., the dose-dependency of adverse events. The finding of a “dose-response,” that is, a higher frequency of adverse events at lower subject weight, suggests (but does not prove) that an adverse event is drug-related.

Using the manual, blinded analysis of the edited line listings for common adverse events, CDER assessed the frequencies of adverse events by subject weight quintile. Of note, some groupings of events were constructed on the basis of common pathophysiologic mechanisms, as well as indistinguishable symptom descriptions (e.g., fatigue and malaise; cold, head cold, URI, etc.).

The numbers displayed in Table 37 represent numbers of subjects with a particular event. Given that the numbers of subjects, and therefore the denominators, in each quintile are approximately equal, higher event numbers in the lower weight quintiles (and lower event numbers in the higher weight quintiles) are indicative of a more persuasive dose-response relation.

For each adverse event or event grouping, the strength of association was assessed using a least-squares approach (i.e., the slope of the relation between numbers of events and numerical quintile). Adverse events (and adverse event groupings) are listed in order of decreasing strength of the “dose-response” relation, within Study 1801.

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It is important to recognize that females are over-represented at lower weight quintiles; males are over-represented at upper weight quintiles. Thus, events that tend to be more common in females, e.g., urinary tract infection, cystitis, etc., as well as those that occur exclusively in females, e.g., vaginitis, dysmenorrhea, etc., appear to show a dose-response. In this case, however, these signals were spurious, in that they largely vanished when data from females were analyzed separately (see Table 37, bottom).

Most concerning regarding the analyses in Table 37 is the strength of the dose-response relation for the 3 upper rows of adverse events. For all 3 of these events/categories ("flu," upper respiratory infection; general infection; headache), the "dose-response" is evident in both Studies 1801 and 1802. Moreover, the "dose-response" is not evident in the control groups. Taken together, these analyses suggest (but do not prove) that the associations between infections and natalizumab, as well as headaches and natalizumab, are causally-related.

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**Table 37: Dose-Dependency of Adverse Events – CDER Analysis**

weight quintile --> (1 = low; 5 = high)	Study 1801										Study 1801									
	Natalizumab					Placebo					Natalizumab + Avonex					Placebo + Avonex				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
nasopharyngitis, nasal congestion, sore throat	87	131	77	54	68	37	34	43	43	54	43	41	71	35	30	46	71	44	44	54
infection	90	100	91	66	77	40	45	52	51	53	47	39	47	33	34	56	42	45	52	56
urinary tract infection	23	29	21	10	8	14	16	14	7	7	12	11	9	5	4	24	11	11	11	13
migraine	10	9	5	1	3	4	4	4	4	3	3	3	5	3	2	9	3	4	7	9
bronchitis, tracheitis, chest cold	16	19	11	10	10	3	8	7	6	6	7	7	7	7	6	9	3	6	7	10
urinary urgency and incontinence	22	27	18	15	18	19	17	16	13	18	8	9	7	7	5	16	19	17	20	19
cystitis	7	6	5	2	1	1	0	0	0	0	1	4	3	0	0	1	0	0	0	0
abdominal discomfort	18	15	14	12	12	4	7	14	8	9	5	7	6	3	10	7	5	9	7	9
weakness/fatigue	23	34	24	17	24	21	17	22	21	20	11	16	12	12	15	28	18	21	17	19
nausea, vomiting	23	24	23	10	23	14	11	13	12	16	15	11	10	8	7	18	12	15	10	7
constipation	15	9	12	4	11	9	10	16	9	8	8	7	7	3	4	13	10	13	11	8
impaired mobility, weakness	6	6	4	1	2	3	4	1	2	5	0	1	1	1	5	3	2	2	2	2
vertigo	9	16	11	5	8	6	6	8	8	11	3	6	3	5	3	6	8	8	7	4
ovarian cysts and pain	6	0	1	0	0	0	1	1	0	2	1	0	0	0	1	2	0	1	0	1
ataxia	3	9	3	3	0	5	6	3	5	4	4	3	3	1	1	5	8	5	7	7
stiffness	15	26	16	10	16	15	16	13	12	12	2	10	9	12	9	10	9	10	7	17

\* Events and quintiles based on females, only

* vaginal dryness	6	9	5	2	9	4	4	3	3	3	5	1	1	2	0	6	4	4	8	6
* menstrual irregularity	6	9	5	7	4	2	3	3	4	4	1	0	1	3	2	4	4	1	0	3
* dysmenorrhea	4	2	3	0	2	4	1	2	3	2	0	0	0	0	1	2	3	1	3	3
* ovarian cysts and pain	4	2	0	1	0	0	1	1	0	2	1	0	0	0	1	2	0	1	0	1



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#### 7.4.2.2 Explorations for Time Dependency for Adverse Findings

The applicant provided analyses of the time of occurrence of adverse events relative to the time of administration of the study agent. CDER reviewed this data for Study 1801, Study 1802, and combined results from Studies 1801 and 1802. Hypersensitivity reactions and infusion reactions occurred close to the time of study agent administration. This review did not detect any other clear association between any adverse event and the time of the most recent study agent administration.

#### 7.4.2.3 Explorations for Drug-Demographic Interactions

The study population, like the disease population, is almost exclusively Caucasian; subjects are largely adults in their fourth or fifth decade. Thus, exploratory safety analyses for drug-demographic interactions based on race and/or age are unlikely to be fruitful. Moreover, given the age of the typical MS patient, important co-morbidities that might be expected to impact pharmacokinetics and safety (i.e., diabetes, renal and hepatic insufficiency) are uncommon, making such explorations impracticable.

CDER explored the safety database for drug-gender interactions (Table 38), using the adverse events that appear to constitute a concern, based on the review of common adverse event rates.

There are no trends to suggest a gender-specific susceptibility to adverse events (other than urinary tract infection, which is more common in females).

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**Table 38: Relation Between Gender and Common Adverse Events**

**Study 1801**

	Females		Males	
	Natalizumab n=449	Placebo n=208	Natalizumab n=178	Placebo n=104
infection, bacterial	72 (16%)	37 (17.8%)	25 (14%)	16 (15.4%)
depression	92 (20.5%)	32 (15.4%)	26 (14.6%)	17 (16.3%)
headache	180 (40.1%)	74 (35.6%)	49 (27.5%)	23 (22.1%)
fatigue/malaise	163 (37.4%)	60 (28.8%)	58 (32.6%)	27 (26%)
elevated LFTs	21 (4.7%)	10 (4.8%)	11 (6.2%)	2 (1.9%)
urinary tract infection	82 (18.3%)	35 (16.8%)	9 (5.1%)	16 (15.4%)

**Study 1802**

	Females		Males	
	Natalizumab + Avonex n=442	Avonex n=420	Natalizumab + Avonex n=147	Avonex n=162
infection, bacterial	47 (10.6%)	43 (10.2%)	7 (4.8%)	10 (6.2%)
depression	64 (14.5%)	56 (13.3%)	20 (13.6%)	18 (11.1%)
headache	134 (30.3%)	126 (30%)	29 (19.7%)	27 (16.7%)
fatigue/malaise	144 (32.6%)	166 (39.5%)	46 (30.6%)	40 (24.7%)
elevated LFTs	7 (1.6%)	11 (2.6%)	7 (4.8%)	9 (5.6%)
urinary tract infection	57 (12.9%)	63 (15%)	1 (0.7%)	4 (2.5%)

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#### 7.4.2.4 Explorations for Drug-Disease Interactions

The study population consisted almost entirely of patients with relapsing-remitting MS who met McDonald criterion 1 for diagnosis. Additional exploratory safety analyses for a drug – disease interaction are unlikely to be reliable and are not warranted.

#### 7.4.2.5 Explorations for Drug-Drug Interactions

Study 1802 administered the combination of natalizumab and an interferon- $\beta$  to study subjects. The adverse event profile associated with natalizumab in Study 1802 was similar to the adverse event profile of natalizumab in Study 1801 (see Section 7.1.5.4, Common adverse event tables).

Study 1803 administered the combination of natalizumab and glatiramer acetate (Copaxone<sup>®</sup>) to MS subjects. Study 1803 included only 110 subjects randomized equally to two arms, with study agent administration for only 6 months (see Section 10.1.2, Study 1803). This study did not provide evidence of safety concerns beyond those adverse events associated with natalizumab in Studies 1801 and 1802. However, due to the relatively small sample size and brief study duration, Study 1803 provides only limited data regarding the safety of the combination of natalizumab and glatiramer acetate.

Natalizumab is associated with an increased risk of some types of infection (see Section 7.3.1, Infections, and Section 7.1.5.4, Common adverse event tables). Patients with MS often receive short courses of steroids as treatment of relapses. Corticosteroids can increase the risk of infections. The applicant provided several analyses of the incidence of infection for subjects who received natalizumab without any administration of steroids compared to the incidence of infection for subjects who received both natalizumab and at least one course of steroids. These analyses were provided separately for Studies 1801 and 1802, and included analyses for any infection, any infection within 3 months of steroid administration, and any infection within one month of steroid administration. These analyses do not suggest increased risk of infection from the combination of natalizumab with a short (three to five day course) of corticosteroids (see Section 6.1.3.1.1, Study 1801 – Design).

#### 7.4.3 Causality Determination

Adverse events that are most clearly associated with natalizumab administration include hypersensitivity reactions, depression, infections, and menstrual disorders.

- Hypersensitivity reactions. The consistent relationship of hypersensitivity reactions to immunogenicity (see Section 7.1.10, Immunogenicity), and the consistency of these hypersensitivity reactions in the natalizumab groups in Studies 1801 and 1802, provide strong evidence that natalizumab administration is causative.
- Depression. Although the increased incidence of depression associated with natalizumab was small (see Section 7.1.5.4, Common adverse event tables), the consistency of the

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association in both Phase 3 studies (1801 and 1802) provides some evidence that natalizumab administration is causative.

- **Menstrual irregularities.** The consistency of the association of natalizumab with several different types of menstrual disorders (dysmenorrhea, amenorrhea, and menstrual irregularities), in three separate studies (1801, 1802, and 1803) (see Section 7.1.5.4, Common adverse event tables, and Table 40), provides strong evidence that natalizumab administration is causative.
- **Infections.** Although the increased incidence of infections associated with natalizumab administration in Study 1801 is small, an increase in clinical infections is predicted based on natalizumab's proposed mechanism of action (see Section 2.4, Important Issues With Pharmacologically Related Products). This increased risk of infections is not consistent across studies (see Section 7.1.5.4, Common adverse event tables, Table 23) but there is a dose-response relation for infections that suggests causality (Table 37).
- **For other adverse events, including elevations in liver function tests, fatigue, local bleeding, and syncope, the data are weak (very small numbers of adverse events) and/or inconsistent. Strong evidence of natalizumab causation is lacking.**

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

Study 231 compared administration of two dose levels of natalizumab (3 mg/kg and 6 mg/kg) to placebo in a multicenter, double-blind, randomized, placebo-controlled, 3-arm study (10.1.1, Study 231). Based on the results of Study 231, the sponsor decided that there was no substantial difference in either safety or efficacy between 3 mg/kg and 6 mg/kg of natalizumab. Subsequent clinical studies of natalizumab have administered a fixed dose of 300 mg every 4 weeks. Exploratory analyses of Studies 1801 and 1802 did not provide substantial evidence that weight-adjusted dosing would provide increased efficacy or safety (see Section 6.1.4.3.1, Primary Endpoint, Subgroup Analyses, and Section 7.4.2.1, Explorations for dose dependency for adverse findings).

The regimen of natalizumab administration every 4 weeks has been used in all large and moderately-sized MS studies of natalizumab, including Studies 231, 1801, 1802, and 1803. This regimen is based on pharmacokinetic and pharmacodynamic studies (see Section 5, Clinical Pharmacology and Dr. Iftexhar Mahmood's Clinical Pharmacology review of this application). However, the sponsor has not provided any substantial clinical trials of alternative dosing regimens.

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## 8.2 Drug-Drug Interactions

In Studies 1 and 2, short-term treatment of relapses with corticosteroids was not associated with an increased rate of infection. The safety and efficacy of natalizumab in combination with other immunosuppressive agents have not been evaluated. Patients receiving these other agents should not receive concurrent therapy with natalizumab because of the possibility of increased risk of infections.

After multiple dosing, interferon  $\beta$ -1a (Avonex<sup>®</sup>) reduced natalizumab's clearance by approximately 30%. Given that the adverse event profiles were similar in Study 1801 (without interferon  $\beta$ -1a) and Study 1802 (with interferon  $\beta$ -1a), the data suggest that natalizumab dose reduction is not necessary to avoid enhanced toxicity during co-administration of an interferon beta. (See Section 5.1, Pharmacokinetics, and Dr. Iftekhar Mahmood's Clinical Pharmacology review of this application.)

Results of studies in multiple sclerosis patients taking natalizumab and concomitant beta-interferon (Avonex<sup>®</sup>) or glatiramer acetate are inconclusive with regard to the need for dose adjustment of the beta-interferon or glatiramer acetate (see Section 5.1, Pharmacokinetics, and Dr. Iftekhar Mahmood's Clinical Pharmacology review of this application).

No data are available on the effects of vaccination in patients receiving natalizumab (see Sections 7.2.7, Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study, and 9.3.2, Required Phase 4 Commitments).

## 8.3 Special Populations

The sponsor has not adequately studied the safety and efficacy of natalizumab in patients with chronic progressive multiple sclerosis, renal insufficiency, or hepatic insufficiency, in patients aged 65 and over, or in women who are pregnant or nursing (see Sections 7.2.7, Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study, and 9.3.2, Required Phase 4 Commitments).

Natalizumab should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking natalizumab, discontinuation of natalizumab should be considered. It is not known whether natalizumab is excreted in human milk. Because many drugs and immunoglobulins are excreted in human milk, and because the potential for serious adverse reactions is unknown, a decision should be made whether to discontinue nursing or natalizumab, taking into account the importance of therapy to the mother.

## 8.4 Pediatrics

Safety and effectiveness of natalizumab in pediatric multiple sclerosis patients below the age of 18 have not been studied (see Section 2.5.3, Pediatric Waiver).



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## **8.5 Advisory Committee Meeting**

This application has not been discussed at a CDER advisory committee meeting.

## **8.6 Literature Review**

This review does not include a comprehensive review of the literature on natalizumab.

## **8.7 Postmarketing Risk Management Plan**

The applicant did not submit a proposed postmarketing risk management plan.

## **8.8 Other Relevant Materials**

Review of this application included consultations from the Office of Drug Safety and the Division of Drug Marketing, Advertising, and Communications (DDMAC).

# **9 OVERALL ASSESSMENT**

## **9.1 Conclusions**

- a. Natalizumab has an acceptable safety profile (see Section 7, Integrated Review of Safety) for the treatment of patients with relapsing forms of MS. This assessment is based on placebo-controlled data from 1617 subjects, primarily in Studies 1801 and 1802, with a median of 20 months of natalizumab exposure.
- b. Natalizumab is effective (see Section 6, Integrated Review of Efficacy) for the treatment of patients with relapsing forms of MS, to reduce the frequency of clinical exacerbations. This assessment is based on effect size, statistical persuasiveness, and substantiation across two adequate, and well-controlled investigations. Natalizumab was associated with a decrease (66% relative reduction, 49% absolute reduction) in the relapse rate in Study 1801, and a decrease (54% relative reduction, 42% absolute reduction) in the relapse rate in Study 1802. Both of these Phase 3 studies are relatively large, multicenter, randomized, double-blind, placebo-controlled studies that provide statistically persuasive evidence of benefit. The consistency of natalizumab's effect across multiple endpoints and multiple subgroups, combined with statistically robust results in two well-designed confirmatory studies, provides compelling evidence of efficacy. The overall assessment is based on data from approximately one year of treatment in Studies 1801 and 1802.
- c. Natalizumab is immunogenic (see Section 7.1.10, Immunogenicity), and the immunogenicity impacts negatively on both the safety and efficacy of natalizumab. The safety and efficacy of natalizumab are uncertain for patients who are persistently antibody-positive.



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- d. Adverse events most clearly related to natalizumab administration include hypersensitivity reactions, some infections, menstrual disorders, and depression (see Section 7, Integrated Review of Safety). Most adverse events were mild.
- e. The safety and efficacy of natalizumab beyond 1 year are unknown.
- f. The safety and efficacy of natalizumab have not been established in patients with chronic progressive multiple sclerosis, renal insufficiency, or hepatic insufficiency, in patients aged 65 and over, or in women who are pregnant or nursing.

## 9.2 Recommendation on Regulatory Action

The clinical review recommendation is for accelerated approval of natalizumab for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations. Accelerated approval permits marketing approval based on a surrogate endpoint that is reasonably likely to predict a clinically meaningful benefit.

This recommendation acknowledges that the proposed pivotal studies provide direct evidence of a benefit for only one year of natalizumab administration. The clinical meaningfulness of a decrease in the incidence of relapses at one year is uncertain. Drugs currently approved for this indication have each provided evidence of a benefit at two years in order to gain marketing approval. However, the effect of natalizumab on relapse rate in Study 1801 was approximately twice the effect observed with current first-line drugs for this indication (see Section 2.2.1, Immune Modulators Approved for Treatment of MS). Such comparisons of different agents across studies are problematic, and the public would be best served by direct comparison of natalizumab with available agents. However, the magnitude of natalizumab's effect is sufficient that the effect at one year is reasonably likely to predict a clinical benefit at two years. In this analysis, the effect at one year serves as a surrogate for the effect at two years. This evidence of effectiveness has the limitations of a surrogate, particularly the difficulty in reliably predicting the durability of natalizumab's effect at two years in the ongoing studies. Therefore, completion of the ongoing studies is essential to verify the safety and efficacy of natalizumab.

Accelerated approval requires that the new drug provides evidence of meaningful therapeutic benefit over existing treatments. Many MS patients continue to have exacerbations while taking one of the available first-line MS therapies. None of the currently available therapies have proven efficacy when used as an add-on therapy for these patients. Study 1802, and to a lesser extent Study 1803 (see Section 10.1.2, Study 1803), provide persuasive evidence that natalizumab is effective as an add-on therapy for subjects who continue to have relapses while on a first-line therapy. Therefore, natalizumab has the potential to address an unmet medical need.

The primary safety issue appears to be immunogenicity, which will require further investigation.

The recommended dose of natalizumab is 300 mg IV infusion every four weeks. Natalizumab should be infused over approximately one hour, with observation of the patients during the

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infusion and for 1 hour after the infusion is complete. The infusion should be promptly discontinued upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction.

### **9.3 Recommendation on Postmarketing Actions**

#### **9.3.1 Risk Management Activity**

No special risk management activities are recommended for the marketing of natalizumab.

#### **9.3.2 Required Phase 4 Commitments**

The following are recommended requests to the applicant for clinical postmarketing commitments. The first recommendation relates to the need to have improved data on the interaction of natalizumab with glatiramer acetate, an available first-line therapy for MS.

1. Please commit to conducting a pharmacokinetic study of at least 6 months duration to assess whether chronic administration of natalizumab in combination with glatiramer acetate results in a drug interaction that suggests the need for a dose adjustment of natalizumab.

The following commitment is an exploration of a potential problem with IgG4 monoclonal antibodies. Because natalizumab is the first IgG4 monoclonal antibody approved for chronic administration, the applicant is requested to explore the existence of this potential problem (see Section 2.4, Important Issues With Pharmacologically Related Products).

2. Please commit to conducting a pharmacokinetic study of the interaction of natalizumab with another IgG4 antibody to assess the generation of dual-specificity antibodies targeting both  $\alpha$ 4-integrin and the target of the other antibody.

The next two recommended commitments are components of the accelerated approval process (see Section 9.2, Recommendation on Regulatory Action).

3. Please commit to verifying that the clinical benefit of reduction in exacerbations is sustained with continued natalizumab administration. This will be accomplished by completing the ongoing studies C-1801 and C-1802 through the planned two years and submitting the results along with appropriate labeling changes.
4. Please commit to further evaluating the safety of natalizumab and the efficacy of natalizumab on physical disability. This will be accomplished by completing the ongoing 2-year studies (C-1801 and C-1802) and submitting the study results, including all safety and efficacy data, for all study subjects through Week 128 or subject withdrawal. Appropriate labeling changes will be proposed as part of this submission.

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Many patients with MS are women of child-bearing potential. Therefore, the safety of natalizumab in pregnancy is a critical issue for many MS patients.

5. Please commit to conducting a pregnancy registry, with concurrent controls, for women who become pregnant while exposed to natalizumab to identify the pregnancy outcome and postnatal health status of the children. This commitment includes submitting a revision to the label, once the design of the registry is finalized, that informs patients and physicians of the registry.

The next recommendation is for a postmarketing commitment to assess the mechanism of action of natalizumab (see Section 2.1, Product Information). This commitment reflects the need to have a better understanding of the activity of a new drug for which there is no mechanistically similar drug previously on the market.

6. Please commit to conducting a study to measure the effects of at least a six-month course of natalizumab on immune responses in subjects with relapsing forms of MS that evaluates the effect of natalizumab on percentages of lymphocytes including CD3+, CD4+, CD8+, as well as B and NK cells, and the associated  $\alpha$ 4 integrin expression and binding site saturation.

The next two commitments are for postmarketing commitments to explore the effect of natalizumab, as an immunosuppressant, on the response to neoantigens and recall antigens (see Section 8.2, Drug-Drug Interactions).

7. Please commit to conducting a study of the effect of natalizumab on neoantigen immunization with respect to interval from dosing and the potential for induction of tolerance and assessment of tolerance using a series of two booster immunizations post-natalizumab clearance. If such a study provides evidence that natalizumab has an effect on neoantigen immunization, please commit to conducting a study of the effect of natalizumab on patient response to a neovaccination after withdrawal of natalizumab treatment.
8. Please commit to conducting a study of the effect of natalizumab on recall antigen responses in a chronic dosing situation, including the levels of antibody to the recall antigen and the ability of a booster immunization to raise antibody levels.

The following recommendations are for postmarketing commitments to assess the immunogenicity of natalizumab (see Section 7.1.10, Immunogenicity). The available database provides evidence that immunogenicity is an issue that impacts the safety and efficacy of natalizumab. However, the clinical meaningfulness of this immunogenicity has not been adequately established and requires further investigation.

9. Please commit to using new binding and neutralizing assays to conduct a study of the development and general time course of immunogenicity at any level of titer, and the relationship of natalizumab immunogenicity to safety events.

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10. Pending the development of a new assay for antibodies to natalizumab, please commit to using your current assay to assess the immunogenicity of natalizumab by conducting a study of patients who are at least three months post-treatment so that no assay interfering natalizumab is present in serum. You will analyze this immunogenicity data with consideration of the reasons for discontinuing natalizumab and the adverse event profile of the subjects.

For CMC postmarketing commitments, see the review of this application by Drs. Elena Gubina, Joseph Kutza, and Lei Zhang. For toxicology postmarketing commitments, see the Non-clinical Toxicology review of this application by Dr. Barbara Wilcox.

#### 9.3.3 Other Phase 4 Requests

There are no additional requests.

### 9.4 Labeling Review

Discussions between the applicant and CDER have resolved all major issues with regard to the label.

The applicant initially proposed the trade name of "Antegren." However, the Division of Medication Errors and Technical Support (DMETS) reviewed the proposal and found a potential for medication errors, particularly the potential for confusion of Antegren with Integrilin and Ativan. The applicant then proposed the trade name of However, DMETS reviewed the new proposal and found a potential for medication errors, particularly the potential for confusion of Antegren with Integrilin. The applicant then proposed, and DMETS approved, the trade name "Tysabri."

### 9.5 Comments to Applicant

None.

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## 10 APPENDICES

### 10.1 Review of Individual Study Reports

#### 10.1.1 Study 231

**Title:** A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Safety, Tolerability and Dose Evaluation Study of Intravenous Antegren™ (natalizumab) at Two Dose Levels Using Magnetic Resonance Imaging in Subjects with Multiple Sclerosis

**Objectives:** To assess the effect of natalizumab on brain lesion activity assessed by MRI in subjects with RRMS or SPMS.

**Design:** This was a multicenter (26 centers), double-blind, randomized, placebo-controlled, parallel-group study. Subjects were randomized in a 1:1:1 ratio to placebo, 3 or 6 mg/kg natalizumab IV every 4 weeks for a total of six doses, with follow-up for a total of 12 months.

**Enrollment criteria:** Study inclusion criteria required that subjects have a diagnosis of clinically or laboratory-supported definite relapsing-remitting or secondary-progressive MS; a history of at least 2 MS relapses within the previous 2 years; a baseline EDSS  $\geq 2.0$  and  $\leq 6.5$ ; a minimum of three lesions on T2-weighted MRI of the brain; and no concomitant treatment with immunosuppressant agents.

**Treatment:** Placebo or natalizumab (either 3 mg/kg or 6 mg/kg) IV once every 4 weeks for up to 20 weeks.

**Study Conduct:** 214 subjects were randomized; 213 subjects received at least 1 dose; 195 (92%) of subjects received all 6 doses. Of the 213 who were randomized and dosed, 71 received placebo, 68 received 3 mg/kg natalizumab, and 74 received 6 mg/kg natalizumab.

**Baseline Characteristics:** Females accounted for 65% of the placebo group, 69% of the 3 mg/kg group, and 80% of the 6 mg/kg group. With the exception of gender, the treatment groups were balanced with respect to demography. Age ranged from 22 to 66 years (median 44 years); 152 subjects (71%) were women; 188 subjects (88%) were Caucasian. Weight ranged from 48 to 102 kg (median 69 kg). Treatment groups were balanced with respect to baseline disease characteristics.

**Efficacy Results:** Natalizumab administration was associated with the following:

- a marked reduction in mean number (9.6 in placebo group, 0.6 in 3.0 mg/kg group, 1.2 in 6.0 mg/kg group) of new gadolinium enhancing lesions at 6 months, ( $p < 0.001$ ),

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comparing each natalizumab group individually to placebo, Wilcoxon-Mann-Whitney test);

- no effect on EDSS at 6 months;
- significant decrease in proportion of patients with an MS exacerbation (38% placebo, 19% 3 mg/kg, 19% 6 mg/kg;  $p=0.02$ , comparing each natalizumab group to placebo, Fisher's Exact Test).

**Safety results:** One subject in the placebo group died during the study due to pleural carcinomatosis complicated by hemothorax. Twenty-four subjects experienced serious adverse events: 9 (13%) in the placebo group, 11 (16%) in the 3 mg/kg natalizumab group, and 4 (5%) in the 6 mg/kg natalizumab group. The most common serious adverse events were MS relapses, experienced by 5 subjects (7%) in the placebo group, 4 subjects (6%) in the 3 mg/kg natalizumab group, and no subjects in the 6 mg/kg natalizumab group.

Other serious adverse events were 3 accidental possible overdoses and 3 immune-mediated reactions in the natalizumab groups, (1- anaphylactoid; 1- chest pain, fever, shortness of breath, respiratory infection, lymphadenopathy, otitis media; 1- urticaria and bronchospasm), and 1 immune-mediated reaction in the placebo group (lymphadenopathy, fever, hypersensitivity skin reaction, facial and arm numbness).

The incidence of adverse events that were 5% higher in any natalizumab group compared to placebo is presented in Table 39.

**Table 39: Adverse Events  $\geq 5\%$  More Common in Any Natalizumab Group**

	Placebo	3 mg/kg	6 mg/kg	Total Natalizumab
No. of subjects dosed, (n, %)	71 (100)	68 (100)	74 (100)	142 (100)
Infection	16 (23)	20 (29)	21 (28)	41 (29)
Accidental injury	14 (20)	13 (19)	20 (27)	33 (23)
Flu syndrome	9 (13)	12 (18)	9 (12)	21 (15)
Rash	6 (8)	10 (15)	11 (15)	21 (15)
Back pain	6 (8)	8 (12)	11 (15)	19 (13)
Sinusitis	5 (7)	10 (15)	6 (8)	16 (11)
Diarrhea	5 (7)	9 (13)	4 (5)	13 (9)
Fever	1 (1)	5 (7)	4 (5)	9 (6)
Urinary incontinence	2 (3)	7 (10)	2 (3)	9 (6)
Leg cramps	1 (1)	4 (6)	4 (5)	8 (6)
Flatulence	0	5 (7)	1 (1)	6 (4)
Alopecia	0	4 (6)	1 (1)	5 (4)



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Immunogenicity: Seven subjects (10.3%) in the 3 mg/kg natalizumab group, 8 subjects (10.8%) in the 6 mg/kg natalizumab group, and 1 subject (1.4%) in the placebo group had detectable anti-natalizumab antibodies at any time during the study.

Clinical Pharmacology: Based on the safety and efficacy results from Study 231, and on the pharmacokinetic assessments, the sponsor decided that natalizumab 3 mg/kg and 6 mg/kg dosing were likely to be equally safe and effective, and that fixed dosing, rather than weight-adjusted dosing, of natalizumab would be appropriate for further clinical development. For a discussion of the clinical pharmacology results of this study, see the Clinical Pharmacology review by Dr. Iftekhar Mahmood.

Reviewer's comment: Study 231 provides supportive evidence (to Studies 1801 and 1802) of the efficacy of natalizumab.

#### 10.1.2 Study 1803

Title: A Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Safety Study of Natalizumab in Combination with Glatiramer Acetate (GA) in Subjects with Relapsing-Remitting Multiple Sclerosis (MS)

Objectives: To assess the safety (including immunogenicity) and pharmacokinetics of natalizumab when administered in combination with GA.

Design: This was a multicenter (25 centers), double-blind, randomized, placebo-controlled, parallel-group study. MS patients currently receiving the standard dose and regimen of GA were randomized (1:1) to receive either natalizumab (55 subjects) or placebo (55 subjects) IV every 4 weeks for up to 20 weeks. All subjects continued to receive GA 20 mg SC daily for up to 20 weeks. All subjects had been treated with GA for at least 1 year prior to study entry, and had experienced at least 1 relapse during that time. To preserve blinding, each site had separate treating and evaluating neurologists, with central reading of MRI scans.

Enrollment criteria: Study inclusion criteria required that subjects have a diagnosis of RRMS, meet McDonald criteria 1-4, have a baseline EDSS between 0.0 and 5.0, and have experienced at least 1 relapse (while on GA) within the 12 months prior to randomization. Subjects must have received GA and not received any interferon beta for the 12 months prior to randomization.

Treatment: 300 mg natalizumab or placebo IV once every 4 weeks for up to 20 weeks. All subjects continued to receive GA 20 mg SC daily for up to 20 weeks.

Study Conduct: 110 subjects were randomized and received at least 1 dose; 102 subjects received all 6 doses.

Baseline Characteristics: Median age was 42 years; 84% female; 87% Caucasian; 35% subjects had  $\geq 2$  relapses in the year prior to randomization. The two groups were generally well

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matched; however, the natalizumab group had greater MRI activity at baseline than the placebo group (31% active scans vs. 22%).

Study results are presented in Table 40. The only serious adverse event in the natalizumab group was an elective right hip surgery for treatment of arthritis. The two serious adverse events in the placebo group were an MS relapse and an anaphylactic reaction to GA. There were no hypersensitivity reactions observed with natalizumab infusions.

<b>Table 40: Study 1803 Results</b>	<b>Natalizumab + GA N = 55</b>	<b>Placebo + GA N = 55</b>
Relapse rate (mean, annualized)	0.349	0.649
Proportion of subjects with relapse (n, %)	8 (15)	14 (25)
0 – 1 New gadolinium-enhancing lesions <sup>1</sup> (n, %)	47 (85)	37 (68)
0 – 1 New active lesions <sup>1</sup> (n, %)	45 (82)	35 (64)
Serious adverse events (n, %)	1 (2)	2 (5)
Any adverse events (n, %)	50 (91)	51 (93)
Infections (n, %)	33 (60)	36 (65)
Headache	17 (31)	15 (27)
Back pain	9 (16)	4 (7)
Fatigue	8 (15)	6 (11)
Flushing	6 (11)	1 (2)
Menstrual disorders (n / female N, %)	5 / 50 (10)	3 / 42 (7)
Depression (n, %)	3 (5)	2 (4)

<sup>1</sup> MRI evaluations were performed every 4 weeks. Values provided are cumulative for all study visits. The number of new active lesions at each visit was calculated as the sum of the gadolinium-enhancing lesions and the non-enhancing new or newly enlarging T2 lesions.

**Immunogenicity:** Five subjects (9%) who received natalizumab were persistently antibody-positive, compared to 26% of subjects who were antibody-positive at any time post-baseline. The presence of serum antibodies to natalizumab appeared to be associated with a higher incidence of certain infusion-related adverse events (e.g., flushing, pyrexia, rigors), and MS relapse.

**Reviewer's comment:** This study provides modest evidence of the safety of the co-administration of natalizumab and GA. The study also provides supportive evidence (to Study 1802) that natalizumab will be beneficial as an add-on therapy for patients who have a relapse while receiving a non-interferon therapy for MS. However, because of the short duration of this study, further study would be necessary to confirm the efficacy and safety of natalizumab as an add-on agent for subjects who have a relapse while receiving GA. The study is insufficient to assess whether the co-administration of natalizumab and GA warrants a dose adjustment for either natalizumab or GA (see Clinical Pharmacology review by Dr. Iftekhar Mahmood).

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### 10.1.3 Amendments to Protocols for Studies 1801 and 1802

#### Study 1801 Protocol Amendments

- 1) Initial protocol submitted on September 5, 2001.
- 2) Protocol amendment submitted on January 11, 2002. This amendment contained modifications to the eligibility criteria and modified the treatment of relapses.
- 3) Protocol amendment submitted on September 15, 2003. This amendment rank prioritized the secondary endpoints.
- 4) Final protocol submitted on September 15, 2003.

#### Study 1802 Protocol Amendments

- 1) Initial protocol submitted on January 11, 2002.
- 2) Protocol amendment submitted on September 4, 2002. This amendment contained modifications to the eligibility criteria and rank prioritized the secondary endpoints.
- 3) Protocol amendment submitted on September 16, 2003. This amendment contained several minor revisions to the protocol.
- 4) Final protocol submitted on September 16, 2003.

### 10.2 Line-by-Line Labeling Review

The applicant submitted a draft label that was revised during discussions between the applicant and CDER. After extensive revisions, the proposed label contains an accurate presentation of the known safety and efficacy of natalizumab. The label also provides appropriate directions for the use of natalizumab.

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### 10.3 McDonald Diagnostic Criteria for MS

See McDonald et al, 2001.

Clinical Presentation	Additional data needed for MS Diagnosis
1 – Two or more attacks; objective evidence of 2 or more lesions	None
2 – Two or more attacks; objective evidence of 1 lesion	Dissemination in space, demonstrated by: • MRI*, or • $\geq 2$ lesions on MRI + positive cerebrospinal fluid (CSF)**, or • await clinical attack
3 – One attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by: • MRI ***, or • second clinical attack
4 – One attack; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • MRI*, or • $\geq 2$ lesions on MRI + positive CSF**, or • await clinical attack, and • dissemination in time, demonstrated by: • MRI***, or • second clinical attack

\*MRI must have any three of the following:

- 1 gadolinium-enhancing lesion or 9 T2 hyperintense lesions if there is no gadolinium-enhancing lesion
- $\geq 1$  infratentorial lesion
- $\geq 1$  juxtacortical lesion
- $\geq 3$  periventricular lesions

\*\*Positive CSF determined by oligoclonal bands detected by established methods different from any such bands in serum or by a raised Immunoglobulin G (IgG) index.

\*\*\*MRI must meet the following criteria for dissemination of lesions in time:

- 1) If a first scan occurs 3 months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but 3 months is recommended. A new T2 hyperintense or gadolinium-enhancing lesion at this time then fulfills the criterion for dissemination in time.
- 2) If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new

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gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than 3 months after the first scan that shows a new T2 hyperintense lesion or an enhancing lesion will suffice.

#### **10.4 Kurtzke Expanded Disability Status Scale**

The Expanded Disability Status Scale (EDSS) provides a disability score based on assessment of seven Functional Systems (Pyramidal, Cerebellar, Brain Stem, Sensory, Bowel and Bladder, Visual, and Mental) and ambulation. Functional System (FS) scores are subjective, based on the neurologic examination and/or symptoms. For each FS, a score of 0 is normal, with higher scores, up to a maximum of 5 or 6, indicating increasing dysfunction. EDSS scores from 0-10 are described below:

- 0.0 - Normal neurologic exam [all grade 0 in all FS scores]
- 1.0 - No disability, minimal signs in one FS (i.e., grade 1)
- 1.5 - No disability, minimal signs in more than one FS (more than one grade 1)
- 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1)
- 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1)
- 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory
- 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two grade 3 (others 0 or 1) of 5 grade 2 (others 0 or 1)
- 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps and the patient should be able to walk > 500 meters without assistance or rest
- 4.5 - Fully ambulatory without aid, up and about much of the day, may otherwise require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps and walks > 300 meters without assistance or rest.
- 5.0 - Ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provision).
- 5.5 - Ambulatory without aid or rest for 100 meters; disability severe enough to preclude full daily activities (e.g., to work a full day without special provision).

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6.0 - Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk 100 meters with or without resting.

6.5 - Constant bilateral assistance (canes, crutches, or braces) required to walk 20 meters without resting.

7.0 - Unable to walk at least 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair about 12 hours a day.

7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer; wheels self but unable to carry on in wheelchair a full day.

8.0 - Essentially restricted to chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms.

8.5 - Essentially restricted to bed most of day; has some effective use of arm(s); retains some self-care functions

9.0 - Helpless bed patient; can communicate and eat.

9.5 - Totally helpless bed patient; unable to communicate effectively or eat or swallow

10.0 - Death due to MS.

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## 11 REFERENCES

- Aalberse RC, Schuurman J. IgG4 breaking the rules. *Immunology* 2002; 105(1): 9-19.
- Garcia-Enguidanos A, Calle ME, Valero J, et al. Risk Factors in miscarriage: a review. *Eur J Obstet Gynecol Reprod Biol* 2002; 102:111-119.
- Hochberg, Y. A sharper Bonferroni procedure for the multiple tests of significance. *Biometrika* 1988; 75:800-802.
- Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The INFB Multiple Sclerosis Study Group. *Neurology* 1993; 43:655-661.
- Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996; 39:285-294.
- Johnson KP, Brooks BR et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of phase III multicentre, double-blind, placebo-controlled trial. *Neurology* 1995; 45:1268-1276.
- Kurtzke, JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33:1444-1452.
- Lublin, FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology* 1996; 46:907-911.
- McDonald WI, Compston A, Edan G, Goodkin D, Hartung H-P, et al. Recommended diagnostic criteria for MS. *Ann Neurol* 2001; 50: 121-127.
- Papayannopoulou T, Nakamoto B. Peripheralization of hemopoietic progenitors in primates treated with anti-VLA4 integrin. *Proc Natl Acad Sci USA* 1993; 90:9374-9378.
- Papayannopoulou T, Priestley GV, Nakamoto B, et al. Synergistic mobilization of hemopoietic progenitor cells using concurrent  $\beta 1$  and  $\beta 2$  integrin blockade or  $\beta 2$ -deficient mice. *Blood* 2001; 97(5): 1282-1288.
- Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, et al. New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols. *Ann Neurology* 1983; 13(3): 227-231.
- PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon  $\beta$ -1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; 352:1498-1504.

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Runmarker B, Anderson O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. Brain 1993; 116: 117-134.

## **EXHIBIT 13**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

Food and Drug Administration

## Memorandum

Center for Drug Evaluation and Research  
1451 Rockville Pike  
Rockville, MD 20852

Office of Drug Evaluation VI  
HFD-106

**Date:** November 23, 2004

**From:** David Ross, M.D., Ph.D.; Deputy Director, ODE 6

**Subject:** Deputy Office Director Review of BLA/STN 125104/0  
Natalizumab for relapsing-remitting multiple sclerosis

**To:** BLA 125104/0 File  
Karen Weiss, M.D.; Director, ODE 6

### Identifying information

BLA/STN#: 125104  
Applicant: Biogen Idec  
Biologic name: Natalizumab  
Proposed trade name: Tsyabri  
Submission date: May 24, 2004  
Stamp date: May 24, 2004  
PDUFA goal date: November 23, 2004  
Formulation: 300 mg natalizumab in sterile, single use vials for injection  
Proposed indication: Treatment of relapsing forms of multiple sclerosis  
Proposed regimen: 300 mg intravenous infusion every 4 weeks

**Recommended regulatory action:** Accelerated approval under 21 CFR 601 Subpart E

The primary reviewers, the statistical team leader, and director of the reviewing division have done an excellent job in their respective reviews of analyzing the data in this application, discussing the relevant issues, and drawing scientifically sound conclusions supporting their regulatory recommendations. In this memorandum, I will summarize the review issues presented by this application and address the major issues arising in the review of this application. In summary, I concur with the primary reviewers, statistical team leader, and division director that this application should be granted accelerated approval under the provisions of 21 CFR 601 Subpart E.

**Deputy Office Director Review of BLA/STN 125104–Natalizumab for relapsing-remitting MS****Clinical Background**

Multiple sclerosis (MS) is a chronic, frequently progressive disorder of the central nervous system (CNS) that represents a major cause of disability. Its current prevalence in the United States has been estimated to be at least 350,000 cases (Anderson *et al.* 1992). Disease onset generally occurs in the second to third decade of life and follows a variable course, most often with intermittent relapses (exacerbations) with relative clinical stability between relapses (relapsing-remitting MS). In some patients, symptoms will progress between relapses (secondary progressive MS).

The etiology of MS is poorly understood, but is thought to result from immune-mediated CNS demyelination in genetically susceptible individuals (Noseworthy *et al.* 2000). Autoreactive T cells cross the blood-brain barrier (BBB) via interactions with adhesion molecules, particularly  $\alpha 4$ -integrins. These T cells, along with anti-myelin antibodies, are thought to cause a complex cascade of events that result in destruction of myelin sheaths and scar formation. Affected patients develop hypocellular demyelinated plaques with axonal preservation, particularly in the areas around the optic nerves, periventricular white matter, brain stem, cerebellum, and spinal cord white matter. Areas of active demyelination appear on magnetic resonance imaging (MRI) as gadolinium-enhancing lesions. Diagnosis is classically based on clinically apparent lesions “disseminated in time and space”; standardized criteria (McDonald *et al.* 2001) have been devised for MS diagnosis that now also encourage diagnosis based upon one clinical lesion and MRI evaluations to complete the evidence for dissemination in space and time.

Demyelination in MS prevents saltatory conduction via the nodes of Ranvier, leading to inefficient transmission of action potentials. Clinical manifestations are protean and include sensory disturbances (e.g., paresthesias), ophthalmologic symptoms (e.g., ophthalmoplegia and diplopia due to brainstem involvement), motor disturbances (which may progress to quadriplegia), and cerebral signs and symptoms (e.g., dementia, depression, and seizures).

Available therapies for MS include corticosteroids for acute exacerbations, and interferon-beta or glatiramer acetate for prevention of relapses or progression of disability in the relapsing forms of MS. Although the latter group of agents is safe and effective, a number of randomized, placebo-controlled trials in patients with relapsing-remitting MS have consistently shown that these therapies reduce the relative risk of relapse by about one-third at most. In addition, although the risk-benefit assessment of these agents supports their use, they are associated with potentially serious toxicities. Thus, new therapies for this potentially disabling disease are needed.

**Regulatory Background**

Natalizumab is a recombinant humanized IgG4 $\kappa$  monoclonal antibody that binds to the  $\alpha 4$ -subunit of  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$  integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the  $\alpha 4$ -mediated adhesion of leukocytes to their counter-receptor(s). It is hypothesized that by interfering with leukocyte migration, natalizumab inhibits the migration of activated T cells across the blood-brain barrier, decreasing recruitment of these cells to inflamed parenchyma.

For a full history of significant pre-BLA submission activities, the reader is referred to the various primary reviews. The IND for natalizumab for treatment of relapsing-remitting MS

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was originally submitted on October 23, 1996. Protocols for pivotal Phase 3 trials were submitted in mid-2001. A pediatric waiver was granted on August 2, 2002. A pre-BLA meeting was held with the Applicant on February 17, 2004, at which the Agency agreed to consider an application for accelerated approval. The application was submitted in eCTD format on May 24, 2004, and accepted for filing on July 23, 2004.

**Chemistry, manufacturing, and controls issues**

The reader is referred to the CMC review by Drs. Elena Gubina, Joseph Kutza, and Lei Zhang of the Division of Monoclonal Antibodies. I concur with their conclusion that the manufacture of natalizumab is well controlled, and leads to a product that is pure and potent. Natalizumab is the first IgG4 monoclonal antibody intended for chronic administration. This raises a novel chemistry issue. Some IgG4 molecules have heavy chains that are held together by noncovalent interactions. In the case of natalizumab, — of the molecules have heavy chains linked together in this fashion. Thus, natalizumab has the potential to recombine *in vivo* with IgG4 molecules of different specificity and form bispecific antibodies (Aalberse and Schuurman 2002). Because of the potential effects of such “scrambling” on the safety and efficacy of natalizumab, I concur with the need for a post-marketing commitment to develop and validate bispecific natalizumab IgG4 antibodies in human serum samples. Other issues identified include problems with the current assay used to identify and quantify anti-natalizumab antibodies. However, I concur that these and other CMC issues do not preclude approval and can be addressed via the post-marketing commitments agreed to by the Applicant. The manufacturing facility was found to be in compliance with cGMPs and capable of manufacturing natalizumab drug substance in a consistent manner using validated processes.

**Pre-clinical pharmacology and toxicology issues**

The reader is referred to the pre-clinical pharmacology review by Dr. Anne Pilaro and the pre-clinical toxicology review by Dr. Barbara Wilcox. In pre-clinical studies, the natalizumab administration was generally well tolerated; in single and multiple-dose studies, natalizumab was associated with a reversible increase in circulating leukocytes, an expected effect given the pharmacologic activity of this agent and one seen in clinical studies, as described below under Safety. Natalizumab-associated effects that were seen less consistently included dose-dependent increases in reticulocytes and/or nucleated red blood cells (nRBCs), increased spleen weight, mild to moderate follicular hypertrophy in spleen and lymph node, and minimal to mild focal leukocyte infiltrates in the liver. Mild to moderate glomerulonephritis was seen in one chronic administration study in monkeys along with circulating immune complexes; however, this phenomenon was not seen in another monkey study, and glomerulonephritis was not seen in clinical studies.

In guinea pigs with experimental allergic encephalomyelitis (EAE), a demyelinating disorder used as a pre-clinical model for MS, administration of natalizumab was associated with reduction or reversal in clinical signs of illness. In the guinea pig EAE model, natalizumab treatment was also associated with histopathologic reduction in inflammation and radiologic improvement in demyelinated plaques.

The epidemiology of MS shows a 2:1 female predominance; as mentioned above, disease onset occurs early in adulthood. In addition, embryogenesis could, in theory, be affected by agents such as natalizumab that bind to adhesion molecules such as integrins. Thus, the



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reproductive toxicity of natalizumab represents an important issue in the evaluation of this agent. Non-clinical reproductive toxicology studies demonstrated that treatment with natalizumab has the potential to reduce fertility through impairment of embryonic implantation. In monkeys and guinea pigs a small tendency toward post-implantation loss and decreased fetal survival was noted. In monkeys and guinea pigs, natalizumab was found to undergo transport across the placenta and fetal drug levels were roughly 30% of maternal levels. Infants exposed to natalizumab before birth were born with hematologic findings characteristic of natalizumab exposure (increased WBC, nRBC, increased circulating lymphocytes). However, no teratogenic effects of natalizumab treatment were noted for either guinea pigs or monkeys. Given that the benefits of natalizumab in pregnant women may be acceptable despite its potential risks, and given the lack of human data on the risks of natalizumab treatment during pregnancy, I concur with Dr. Wilcox's recommendation that product labeling indicate natalizumab as being in Pregnancy Category C. The Applicant has agreed to obtain additional data via a registry of pregnant women treated with natalizumab.

**Clinical Pharmacology issues**

The reader is referred to the clinical pharmacology review by Dr. Iftexhar Mahmood. The available data adequately characterize the pharmacokinetics and pharmacodynamics of natalizumab, and support a dosing regimen of 300 mg given intravenously every 4 weeks. In particular, the data submitted support a fixed dose regimen, as opposed to a weight-based dose regimen, for the following reasons. First, a Phase 2, randomized, placebo-controlled multiple-dose study (Study 231) of natalizumab at doses of 3 mg/kg and 6 mg/kg in patients with relapsing-remitting MS showed similar reductions in relapse risk between treatment arms. Second, as discussed below, the pivotal clinical trials (Studies 1801 and 1802) did not show a relationship between patient weight and clinical outcome. Finally, in Study 231, 90% of patients in both dosage arms had serum natalizumab concentrations in excess of 2.5 µg/mL 4 weeks after infusion, a level sufficient to achieve at least 80% α4-integrin saturation.

Other relevant clinical pharmacology issues include interactions of natalizumab with Avonex (interferon-beta) and glatiramer acetate. Avonex appears to decrease clearance of natalizumab by 30%; however, given the similarity in adverse event profiles between populations receiving natalizumab alone (in Study 1801) and those receiving natalizumab in combination with Avonex (in Study 1802), I agree that dosage modification is not indicated in the latter circumstance. Characterization of the interaction between natalizumab and glatiramer acetate is inconclusive, and the Applicant has agreed to a post-marketing commitment to resolve this issue.

**Clinical/statistical issues****Efficacy**

For full details, please see the clinical review by Dr. Wilson Bryan and the statistical review by Dr. Kallappa Koti and the statistical team leader review by Dr. Boguang Zhen. The Phase 3 program consisted primarily of two on-going double-blind, randomized controlled trials, one comparing natalizumab to placebo (Study 1801), the other comparing natalizumab in combination with Avonex (a marketed brand of an interferon-beta) to Avonex plus placebo (Study 1802). Both trials were designed and powered to demonstrate superiority of the

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natalizumab treatment arm to the comparator arm. For full details of study design and conduct, the reader is referred to the primary review by Dr. Bryan.

Study 1801 randomized patients in a 2:1 ratio to natalizumab, 300 mg every 4 weeks, versus placebo. The patients consisted of adults aged 18-50 who met standardized (McDonald) criteria for the diagnosis of relapsing-remitting MS who had had at least one relapse in the 12 months prior to study entry (with resolution at least 50 days prior to study entry), had brain lesions on MRI consistent with MS, and who had a Kurtzke Extended Disability Status Scale (EDSS) score of 0.0 to 5.0. Patients were assessed every 12 weeks and during suspected relapses; the definition of relapses excluded pseudo-exacerbations. The primary endpoint for the one year analysis was the annualized relapse rate,

Study 1801 enrolled 627 patients in the natalizumab arm and 315 in the placebo arm. Patients in the two treatment arms were comparable with respect to demographic characteristics, disease stage and duration, relapse frequency, degree of disability, and number of lesions on MRI. The discontinuation rate was comparable in both arms.

Study 1802 randomized patients in a 1:1 ratio to natalizumab, 300 mg every 4 weeks in combination with Avonex, or to Avonex (plus placebo to maintain the double-blind design). The entry criteria were similar, except that patients had to have previously been receiving Avonex for the 12 months prior to study entry; the 1 year and 2 year endpoints were the same as Study 1801.

Study 1802 randomized 594 patients to natalizumab + Avonex and 602 to Avonex + placebo. Because of exclusion of data from a single site that was closed early, the primary analysis included 582 patients randomized to natalizumab + Avonex and 589 randomized to Avonex + placebo; sensitivity analyses did not show any effect of this exclusion on the overall results. As in Study 1801, patients in the two treatment arms were comparable with respect to demographic characteristics, McDonald criteria class, disease duration, relapse frequency, degree of disability, and number of lesions on MRI. The discontinuation rate was comparable in both arms.

The median patient time on study was 13 months for both Studies 1801 and 1802. Dr. Koti has raised the question as to whether it is valid to describe the results in product labeling with the term “one year data.” This is in large part a terminological issue that does not significantly affect interpretation of the data. As outlined by Dr. Bryan, the original protocols pre-specified an analysis after patients had undergone an average of one year of observation, with subsequent amendment of the protocols to include a pre-specified cut-off date that achieved that criterion. Study 1801 included data on 988 patient-years of observation, while Study 1802 had data on 1268 patient-years of observation; both thus averaged 13 months of observations per patient, and this is reflected in the clinical studies section of the final version of product labeling, which has been agreed to by the Applicant. I concur that this is an accurate description of the nature of these data.

Efficacy results for studies C-1801 and C-1802 are shown in Table 1 for the primary endpoint.

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<b>Table 1. Annualized Relapse Rate, All Subjects</b>				
	Study 1801		Study 1802	
	Placebo N = 315	Natalizumab N = 627	Placebo + Avonex N = 582	Natalizumab + Avonex N = 589
Mean	0.735	0.250	0.780	0.357
Standard Deviation	1.126	0.533	1.002	0.620
Median	0	0	0.685	0
Range				

In study 1801, natalizumab-treated patients had a 66.0% relative reduction in the risk of relapse compared to placebo-treated patients. In study 1802, natalizumab-treated patients had a 54.2% relative risk reduction. This treatment effect of natalizumab was consistent when analyses were stratified by demographic subgroup, weight, geographic location, baseline disability score, baseline relapse rate, McDonald criteria class, baseline number of lesions on MRI, or treatment history. In addition, sensitivity analyses examining the effect of missing data showed a consistent treatment effect in natalizumab-treated patients.

Phase 1 and 2 studies of natalizumab employed a weight-based dosing regimen, while the submitted Phase 3 studies used a fixed dose regimen of 300 mg given every 4 weeks. Dr. Bryan's analyses of the effect of weight on the primary endpoint do not show a consistent relationship between patient weight and relapse frequency in any treatment group; if there were in fact such a relationship, natalizumab should consistently show a lesser treatment effect in heavier patients because of inadequate dosing. Thus, the available data support the proposed fixed dose of 300 mg. However, in Studies 1801 and 1802, natalizumab was administered every 4 weeks, rather than monthly as proposed in the Applicant's draft labeling. Since the clinical results were obtained with this administration schedule, I concur with Dr. Bryan's conclusion that the recommended dosage regimen should be 300 mg given intravenously every 4 weeks, which is reflected in the final version of product labeling and has been agreed to by the Applicant.

Dr. Koti's review raises the issue of whether p values may be appropriately used in product labeling, given complex statistical issues with the Poisson model employed by the Applicant and previously agreed to by the Agency. I concur with Dr. Zhen's statistical team leader review, in which he concludes that use of p values in product labeling is supported by the study design and conduct. Of note, the study design was extensively discussed with Agency clinical and statistical reviewers, including Dr. Koti, prior to study initiation and the Agency agreed that the study design as implemented would support approval. In this regard, I do not agree with Dr. Koti's unsupported assertion that the study design was suboptimal, for the following reasons: a) the study design employed randomization by site as a bias minimization feature; b) for the reasons outlined in Dr. Zhen's review, use of study sites with small numbers of patients is valid, and in fact, exclusion of such sites would have prevented any such study from being performed; and c) Dr. Koti's analysis of five arbitrarily selected sites represents a *post hoc* analysis that does not support his conclusions. Of note, in Dr. Bryan's analysis, when sites with 20 or more enrolled patients were individually examined, a consistent treatment effect was seen

**Deputy Office Director Review of BLA/STN 125104–Natalizumab for relapsing-remitting MS**

in natalizumab-treated patients, although there was some variability because of the small number of patients at any given site.

Tables 2 and 3 show results for two of the secondary endpoints; results for other secondary endpoints were consistent with the results in these tables.

**Table 2. Number of New or Newly-Enlarging T2 Hyperintense Lesions on Year 1 MRI**

	Study 1801		Study 1802	
	Placebo N = 293	Natalizumab N = 600	Placebo N = 485	Natalizumab N = 505
0	70 (24%)	376 (63%)	230 (47%)	392 (78%)
1	41 (14%)	112 (19%)	70 (14%)	69 (14%)
2	23 (8%)	40 (7%)	61 (13%)	24 (5%)
3	24 (8%)	30 (5%)	39 (8%)	10 (2%)
4-9	71 (24%)	34 (6%)	55 (11%)	8 (2%)
10-98	64 (22%)	8 (1%)	30 (6%)	2 (<1%)

**Table 3. Proportion of Subjects Relapse-Free**

	Study 1801			Study 1802		
	Placebo N = 315	Natalizumab N = 627	Relative risk* (95% CI)	Placebo + Avonex N = 582	Natalizumab + Avonex N = 589	Relative risk* (95% CI)
Number relapse -- free	166 (53%)	474 (76%)	1.43 (1.28, 1.61)	265 (46%)	392 (67%)	1.46 (1.32, 1.62)

\* Relative risk of being relapse-free, comparing natalizumab group to placebo group

### Efficacy conclusions

The primary and secondary endpoint results, along with the subgroup and sensitivity analyses performed by the primary reviewers, support the efficacy of natalizumab in decreasing the relapse rate at one year, whether administered as monotherapy or in combination with Avonex. Dr. Walton, in his division director's memorandum, clear and convincingly articulates why this endpoint is reasonably likely to predict clinical benefit over a longer time period and support accelerated approval. I fully concur with his analysis and recommendation.

I will briefly recapitulate the rationale for accelerated approval for this application. One year data is not sufficient to support traditional approval for this indication, given the chronic nature of relapsing-remitting MS, and the potential for lack of durability of the treatment effect. However, accelerated approval under 21 CFR 601 Subpart E is supported by the serious nature of relapsing-remitting MS; the magnitude of the observed treatment effect of natalizumab; the consequent reasonable likelihood that the one year data predicts longer-term clinical benefit; and the potential of natalizumab to represent a meaningful therapeutic benefit to patients over existing treatments. I agree with Dr. Walton's description of the reasons why an early time point can serve as a reasonable predictor of results at a later time point; his analogy with the regulatory basis for accelerated approval of anti-retroviral agents is particularly persuasive, given the durability of benefit issues with that group of therapeutic agents.

Conventional approval will depend on verifying the clinical benefit of natalizumab by demonstrating clinical efficacy at two years. Studies 1801 and 1802, which are currently

**Deputy Office Director Review of BLA/STN 125104–Natalizumab for relapsing-remitting MS**

ongoing, were designed to study the effects of two years of treatment. The Applicant has committed to complete these studies and submit study reports on them, along with revised labeling reflecting the results.

**Safety****Extent of exposure**

The reader is referred to Dr. Bryan's review for full details of the safety analysis. The safety database from placebo-controlled trials for natalizumab includes 2,539 patients; duration of exposure and patient populations exposed are shown in Table 4. The majority of the multiple sclerosis patients were exposed at the proposed recommended regimen. The safety analysis focused on MS patients treated with natalizumab for prolonged periods; other populations, such as Crohn's disease patients or healthy volunteers, were small in size and treated for short durations, and except for serious clinical or laboratory adverse events are unlikely to contribute significantly to understanding of the toxicity profile of natalizumab. The size of the patient population exposed to natalizumab for one year or more is sufficient to detect, with 95% confidence, adverse events occurring at a rate of 0.3% or greater. Given the potential population exposure to natalizumab, this database appears adequately powered to evaluate the safety of natalizumab for purposes of licensure.

<b>Table 4. Total Exposure to Natalizumab in Placebo-Controlled Trials</b>						
	Multiple Sclerosis			Crohn's disease		
	Total	Natalizumab	Placebo	Total	Natalizumab	Placebo
Total N	2752	1617	1135	1178	922	256
Duration of Exposure (weeks)						
1 to <12	376	247	129	1178	922	256
12 to <24	114	63	51	0	0	0
24 to <52	331	184	147	0	0	0
52 to <116	1924	1119	805	0	0	0
≥ 116	7	4	3	0	0	0

**Deaths**

There have been nine deaths in the natalizumab studies conducted to date; three in placebo-treated MS patients, four in natalizumab-treated MS patients, and two in natalizumab-treated Crohn's disease patients. In two of these cases (one malignancy and one infection), there was a possible relationship between natalizumab treatment and a fatal outcome; a third fatal outcome in a natalizumab-treated patient may have represented a suicide, which is of concern given the association between suicide in MS patients receiving interferon. However, I concur with Dr. Bryan's assessment that these cases do not represent a clear safety signal, given the presence of confounding factors (e.g., the association of these events with the underlying disease itself), lack of data (for example, the case of possible suicide may have in fact been a homicide) and the lack of a substantial difference in mortality rates between natalizumab and placebo-treated subjects (0.2% vs. 0.2%), although the size of the placebo-treated population precludes meaningful statistical analysis. However, continued evaluation of these issues via examination of post-marketing surveillance data is warranted.



**Deputy Office Director Review of BLA/STN 125104–Natalizumab for relapsing-remitting MS****Nonfatal clinical serious adverse events (SAEs)**

Rates of nonfatal SAEs are shown in Table 5. I concur with Dr. Bryan's conclusion that there is a signal with regard to hypersensitivity and anaphylactoid events in natalizumab-treated patients. Furthermore, analysis of infections in studies C-1801 and 1802 showed a higher incidence of infections in natalizumab-treated patients (2.1% natalizumab vs. 1.3% placebo in study 1801 and 1.8% natalizumab vs. 1.2% placebo in study 1802); given the mechanism of action of natalizumab, this may reflect immunosuppression in these patients. The events reported do not appear to represent infections due to opportunistic pathogens; however, given the mechanism of action of natalizumab, this issue deserves continued scrutiny, both via post-marketing surveillance and via post-marketing commitments agreed to by the Applicant to more fully characterize the effect of natalizumab on the immune system.

**Table 5. Percent of Subjects with Serious Adverse Events in Placebo-Controlled Trials; Includes All Serious Adverse Events With Incidence  $\geq 1\%$  In Natalizumab Group, And Selected Serious Adverse Events of Interest (From Applicant's Analysis)**

	Multiple Sclerosis*		Crohn's Disease**	
	Natalizumab N = 1617	Placebo N = 1135	Natalizumab N = 922	Placebo N = 256
Any serious adverse event	12.5	15.2	17.4	17.2
Infections and Infestations	1.8	1.6	2.8	3.1
Neoplasms	0.6	1.2	0.9	0.4
Hypersensitivity / Anaphylactoid	0.7	0.2	0.5	0.4
Depression / Suicide attempt	0.6	0.7	0.2	0.8
Cardiac disorders	<0.1	0.4	0.5	0

Dr. Bryan performed additional, treatment-blinded categorization-analyses of non-fatal SAEs occurring in Studies 1801 and 1802 at a rate of 0.5% or more that were more frequent in natalizumab-treated patients, pooling AEs in related groups (e.g., lobar pneumonia, atypical pneumonia) to increase the sensitivity of the analysis. He found that events that were more frequent in natalizumab-treated patients in these studies included infection (including pneumonia and urinary tract infection), allergic reaction, anaphylaxis, and cholelithiasis.

**Dropouts and treatment discontinuations**

Dropouts were less frequent in natalizumab treatment arms in both Studies 1801 and 1802 (1801: 3% natalizumab vs. 6% placebo; 1802: 5% natalizumab vs. 7% placebo). Treatment discontinuations were also less frequent in natalizumab-treated patients (1801: 7% natalizumab vs. 9% placebo; 1802: 10% natalizumab vs. 12% placebo). The majority of natalizumab-treated patients who withdrew did so for adverse events, and the majority of these represented urticaria, anaphylaxis, and hypersensitivity reactions, depression or suicidal ideation, and infection, AEs that were more common overall in natalizumab-treated patients.

**Common clinical adverse events**

Rates of common adverse events in Studies 1801 and 1802 are shown in Table 6.



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<b>Table 6. Rates of common adverse events in Studies 1801 and 1802</b>				
	Study 1801		Study 1802	
	Natalizumab N=627	Placebo N=315	Natalizumab + Avonex N=601	Placebo + Avonex N=595
Infection	424 (68%)	200 (63%)	241 (40%)	251 (42%)
Headache	229 (37%)	97 (31%)	163 (27%)	153 (26%)
Fatigue or malaise	226 (36%)	87 (28%)	189 (31%)	206 (35%)
Depression	122 (19%)	49 (16%)	84 (14%)	74 (12%)
Arthritis/arthralgia	107 (17%)	42 (13%)	98 (16%)	85 (14%)
Urinary urgency	65 (10%)	26 (8%)	67 (11%)	69 (12%)
Urinary tract infection	91 (15%)	41 (13%)	98 (16%)	85 (14%)
Rhinitis, congestion, stuffiness	85 (14%)	37 (12%)	59 (10%)	44 (7%)
Abdominal discomfort	71 (11%)	31 (10%)	42 (7%)	37 (6%)
Rash	58 (9%)	22 (7%)	38 (6%)	41 (7%)
Gastroenteritis	56 (9%)	16 (5%)	51 (8.5%)	43 (7%)
Infection, viral	32 (7%)	9 (4%)	20 (5%)	28 (6%)
Vaginitis*	32 (5%)	10 (3%)	1 (0.2%)	3 (0.5%)
Elevated ALT/AST/GGT	31 (7%)	7 (3%)	16 (4%)	12 (3%)
Tonsillitis	27 (4%)	7 (2%)	24 (4%)	19 (3%)
Menstrual irregularities*	27 (4%)	7 (2%)	18 (3%)	26 (4%)
Pruritus	27 (4%)	9 (3%)	25 (4%)	13 (2%)
Chest discomfort	26 (4%)	9 (3%)	28 (5%)	23 (4%)
Dermatitis	24 (4%)	4 (1%)	15 (2%)	23 (4%)
Tremor	18 (3%)	3 (1%)	16 (3%)	2 (0.3%)
Miscellaneous allergic reaction	17 (3%)	4 (1%)	11 (2%)	1 (0.2%)
Rigors	17 (3%)	5 (2%)	10 (2%)	7 (1%)
Syncope	13 (3%)	1 (0.5%)	9 (2%)	17 (4%)
Bleeding	9 (2%)	0	1 (0.2%)	4 (1%)
Dysmenorrhea*	424 (68%)	200 (63%)	241 (40%)	251 (42%)
Amenorrhea*	229 (37%)	97 (31%)	163 (27%)	153 (26%)

\* percentage based on female N

Among AEs rated as severe, infections occurred more frequently in natalizumab-treated patients than in the placebo group in Study 1801 (3.5% vs. 2.5%) and Study 1802 (5.8% vs. 4.9%). However, as noted by Dr. Bryan, the infections in natalizumab-treated patients resolved spontaneously or responded to appropriate anti-microbial therapy. In the two studies, there were 7 malignancies in natalizumab-treated patients and 5 in placebo-treated patients (0.5% vs. 0.7%); thus, the data did not demonstrate an association between natalizumab and malignancy, but given the immunomodulatory activities of this agent, continued evaluation of this issue via post-marketing surveillance is warranted.

Infusion-related reactions, an AE characteristic of monoclonal antibodies, occurred in both studies at higher rates in natalizumab-treated patients than in placebo-treated patients (1801: natalizumab 20% vs. placebo 15%; 1802: natalizumab + Avonex 21% vs. placebo + Avonex 16%), with headache being the most common infusion-related reaction.

Analyses of disability progression did not show any adverse effect of natalizumab. In addition, data from a Phase 2 study (Study 231) involving treatment of patients with natalizumab for 6 months followed by at least 3 months of follow-up did not show evidence for rebound after

**Deputy Office Director Review of BLA/STN 125104–Natalizumab for relapsing-remitting MS**

withdrawal from natalizumab; relapse rates during follow-up were 35% in placebo-treated patients and 33% in natalizumab-treated patients.

**Laboratory analyses**

Because of the mechanism of action of natalizumab, Dr. Bryan performed an extensive series of analyses of hematologic parameters, including measures of central tendency, shifts in laboratory values, and outlier analyses. These showed increases in mean values for all leukocytes, except neutrophils, which do not express  $\alpha 4\beta 1$ -integrin. In addition, subjects showed, on average, an increase in the percentage of peripheral nucleated red blood cells, which may reflect alterations in retention of these cells in the marrow.

There was minimal evidence for hepatotoxicity when natalizumab is administered alone; there was a slightly higher incidence in shift to abnormal transaminase and bilirubin levels in patients receiving natalizumab in combination with Avonex. However, outlier analysis showed similar numbers of severe elevations in liver function test values in Study 1802 (1 patient in the natalizumab + Avonex group, and 2 patients in the placebo + Avonex-treated group).

**Immunogenicity**

As with any immunogenic agent, development of antibodies against natalizumab was of concern because of the potential for effects on efficacy and safety. Results of immunogenicity testing for development of antibodies to natalizumab are shown in Table 7.

<b>Table 7. Development of antibodies to natalizumab</b>		
	Study 1801	C-1802
	Natalizumab	Natalizumab + Avonex
Subjects randomized	627	589
Subjects evaluated	625 (99.7%)	585 (99.3%)
Antibody negative	568 (91%)	516 (88%)
Any positive antibody	57 (9%)	69 (12%)
Transient antibody positive	20 (3%)	31 (5%)
Persistent antibody positive	37 (6%)	38 (6%)
Time to antibody positive = 0-13 weeks	47 (82%)	66 (96%)
Time to antibody positive = 13 – 26 weeks	7 (12%)	3 (4%)
Time to antibody positive = > 26 weeks	3 (5%)	0 (0%)
Anti-Avonex antibody at Week 24	-	18 (3%)

These data show that 9% of patients receiving natalizumab in Study 1801 and 12% in Study 1802 developed antibodies to this agent, either transiently or persistently. Dr. Bryan analyzed the incidence of AEs according to development of anti-natalizumab antibodies, and found a clear relationship between an immunogenic response and infusion reactions, with the incidence of such reactions higher in those patients with persistent seropositivity (18% for antibody-negative patients, 27% for transiently seropositive patients, and 77% for persistently seropositive patients). Allergic reactions also showed an association with seropositivity, while other common AEs did not.

In addition, antibody development was correlated with a decrease in treatment effect, with the loss being greatest in those patients who were persistently positive for anti-natalizumab

**Deputy Office Director Review of BLA/STN 125104–Natalizumab for relapsing-remitting MS**

antibodies. These data underscore the need to obtain long-term data (i.e., 2 year data) to evaluate the durability of response to natalizumab and further characterize its toxicity profile.

**Safety conclusions**

The safety data in this application and Dr. Bryan's analyses, in combination with the efficacy data described above, support the conclusion that natalizumab has an acceptable benefit-risk ratio, warranting accelerated approval. However, further description of the clinical benefit of natalizumab, via collection of two year data, is necessary to fully characterize the toxicity profile of this agent and to support full approval.

**Regulatory conclusions**

In summary, the data in this application support approval under 21 CFR 601 Subpart E for treatment of relapsing-remitting multiple sclerosis at a dosage regimen of 300 mg intravenously every 4 weeks, and provide a basis for construction of product labeling that contains the essential scientific information needed for the safe and effective use of natalizumab. The product labeling should indicate the lack of information about safety and efficacy beyond one year, and contain appropriate warnings regarding the risk of infusion reactions and immunosuppression. The Applicant has agreed to appropriate post-marketing commitments, including collection of two year data to verify the clinical benefit of natalizumab in relapsing-remitting MS

**Literature cited**

Aalberse RC, Schuurman J. IgG4 breaking the rules. *Immunology*. 2002; **105**:9-19.

Anderson DW, Ellenberg JH, Leventhal CM, Reingold SC, Rodriguez M, Silberberg DH. Revised estimate of the prevalence of multiple sclerosis in the United States. *Ann Neurol*. 1992; **31**:333-6.

McDonald WI, Compston A, Edan G. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001 Jul; **50**:121-7.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG.. Multiple sclerosis. *N Engl J Med* 2000; **343**:938-52.

## **EXHIBIT 14**



biogen idec

28 February 2005

«First\_Name\_», «Last\_Name», «Degree»  
«Job\_Title»  
«Company»  
«Address\_1»  
«Address\_2»  
«City», «State» «Zip\_Code»

**VOLUNTARY SUSPENSION OF NATALIZUMAB DOSING IN ALL  
NATALIZUMAB CLINICAL TRIALS**

**NATALIZUMAB SERIOUS ADVERSE EVENTS MCN2005BI003424 and MCN2005BI003076**

Dear Dr. «Last\_Name»:

Biogen Idec and Elan Pharmaceuticals are announcing a suspension of natalizumab dosing in natalizumab clinical trials for multiple sclerosis (MS), Crohn's disease, and rheumatoid arthritis (RA). These actions, which we believe are in the best interest of patients, have been taken in consultation with the FDA. Regulatory agencies worldwide have been informed.

This decision is based on reports of two serious adverse events that have occurred in patients treated with natalizumab in combination with AVONEX<sup>®</sup> (Interferon beta-1a) in clinical trials of multiple sclerosis. These events involve one fatal, confirmed case and one suspected case of progressive multifocal leukoencephalopathy (PML), a rare and frequently fatal demyelinating disease. The results of our investigations of these reports are preliminary, and the companies continue to evaluate these cases and their possible relationship to natalizumab alone or in combination with AVONEX.

The confirmed case of PML (MCN 2005BI003424) was reported from Biogen Idec study C-1808, "An Open-label, Multicenter Extension Study to Evaluate the Safety and Tolerability of Natalizumab in Subjects with Multiple Sclerosis Who Have Completed Studies C-1801, C-1802, or C-1803." The suspected case of PML (MCN 2005BI003076) was reported from Biogen Idec study C-1802, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab, When Added to AVONEX, in Subjects with Relapsing-Remitting Multiple Sclerosis."

**CASE 2005BI003424**

The subject (ID # 142-101) is a 46-year-old female with a past medical history of depression and migraines who participated in and completed study C-1802, receiving 30 doses of natalizumab in combination with AVONEX. Per protocol, the subject had been receiving AVONEX for at least one year prior to enrolling in C-1802. She entered study C-1808 and received 7 doses of open-label natalizumab in combination with AVONEX with the last dose of natalizumab given on 18 January 2005. She received a total of 37 doses of natalizumab in combination with AVONEX.

In December 2004, the subject experienced right-sided weakness and aphasia, which was initially considered an MS relapse. An MRI revealed a left sided 2 cm non-enhancing tumor/infarct lesion. She was treated with two courses of steroids, one in December 2004 and one in January

2005. Her symptoms continued to worsen over the next few weeks with altered mental status and increased spasticity, and she was hospitalized on 12 February 2005. Neurological examination showed a non-responsive subject with right gaze preference, decorticate posturing, upgoing toes, and no gag reflex. An MRI showed "deep white matter, small vessel ischemic changes within the centrum semiovale periventricular regions, high signal throughout portions of the left temporal and left parietal lobes extending across the corpus callosum into the right frontal lobe." This MRI appearance suggested a differential diagnosis that included PML. Complete blood count was significant for a WBC of 14,000 and 29,000 cells/ $\mu$ L on 12 February and 15 February 2005, respectively (normal range 3,500-10,600 cells/ $\mu$ L). A lumbar puncture revealed glucose of 53 mg/dL (normal range 15-45) and protein of 90 mg/dL (normal range 40-70). Viral PCR testing of the cerebral spinal fluid (CSF) was positive for JC virus. HIV testing via Elisa was negative. The subject was treated with intravenous methylprednisolone but her condition continued to decline and she was transferred to a hospice. The subject died on 24 February 2005.

AVONEX neutralizing antibody status and natalizumab antibody status were negative at Baseline and Weeks 24, 48 and 72.

Concomitant medications at the time of the event included vitamins, ranitidine, donepezil, tizanidine, zolpidem, and ibuprofen.

#### **CASE 2005BI003076**

This subject (ID 197119), a 46-year-old male with a history of melanoma, allergies, and Bell's Palsy, participated in study C-1802 and received 28 doses of natalizumab in combination with AVONEX with the last dose of natalizumab given on 13 December 2004.

In December 2004, the subject developed slow thinking, slurred speech and cognitive dysfunction, and a left hemiparesis, which later progressed to include left-sided sensory impairment in early January 2005. An MRI scan in January 2005 showed a right frontal lesion with no gadolinium enhancement, some degree of gray matter involvement, with the lesion extending beyond the right frontal lobe, now also juxtacortical in the insular regions right and left, with no mass effect or edema. He underwent an extensive work-up that included chest X-ray, chest and pelvic CT, PET scan and CSF analysis. The CT scans showed no malignancy. In addition, the subject tested HIV negative via Elisa. The subject underwent a brain biopsy on 16 February 2005. Preliminary results of the biopsy on 24 February 2005 showed a demyelinating process, no vasculitis, no lymphoma, and no evidence of infection or malignancy. Viral PCR testing of the CSF for JC virus is pending. As of 25 February 2005, the subject was clinically worsening.

AVONEX neutralizing antibody status and titer levels are as follows: Baseline level=15, Week 24 was negative, Week 48 level=27, Week 72 level=30, Week 96 and Week 120 are pending. Natalizumab antibody status was negative at Weeks 12, 24, 36, 48, 60 and 72.

Concomitant medications at the time of this event included Levitra, Claritin-D, Benadryl, and Nasarel.

Given the appearance of the current and past MRIs and the subject's clinical course, the investigator believes that this may be PML and is possibly related to natalizumab.

#### **Review of Natalizumab and AVONEX Safety Databases**

In total, approximately 3,000 patients have been treated with natalizumab in clinical trials of multiple sclerosis, Crohn's disease, and rheumatoid arthritis. The two cases described above are the only reports of PML to date in multiple sclerosis patients treated with natalizumab and AVONEX combination therapy. To date, we have received no reports of PML in multiple sclerosis



patients receiving monotherapy with either natalizumab or AVONEX, nor have we received any reports of PML in patients with Crohn's disease or rheumatoid arthritis in natalizumab clinical trials.

**Progressive Multifocal Leukoencephalopathy**

PML is a rare, progressive, demyelinating disease of the central nervous system that primarily affects immuno-compromised patients. PML is caused by activation of JC virus, a polyomavirus that resides in latent form in up to 80% of healthy adults. The factors leading to activation of the latent infection are not fully understood.

The presenting symptoms of PML typically include impaired cognition, cortical blindness, and hemiparesis. PML lesions are hyperintense on T2-weighted MRI scans and usually do not enhance on T1-weighted scans following gadolinium infusion, unlike new MS lesions, which usually enhance for up to 2 months. Most PML patients have multi-focal lesions of the white matter, although some cases may present with a single new lesion, usually without mass effect.

**Biogen Idec and Elan Actions**

We are voluntarily suspending natalizumab dosing in all natalizumab clinical trials for multiple sclerosis, Crohn's disease, and rheumatoid arthritis. We strongly advise that all patients remain in these studies for additional evaluations.

In addition, we require the following actions:

- Immediately notify your Ethics Committee or Institutional Review Board of these cases and provide them with a copy of this letter.
- Immediately evaluate any patient with signs or symptoms of PML.

We will soon provide you with guidance regarding evaluation of all natalizumab trial patients for evidence of PML.

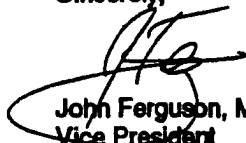
We will provide guidance on possible re-initiation of therapy at a later date.

**Additional Communications**

We are in close contact with FDA and other regulatory authorities. We plan several additional steps and investigations to understand these findings, including convening a panel of scientific experts. We will inform you of important new developments or changes. If you have further questions or require additional information please contact Biogen Idec at 1-888-489-7227.

This report is for your information as an investigator participating in Biogen Idec's MS studies and Elan Pharmaceutical's CD and RA studies. Please review the cases and file the report in the safety section of your natalizumab Investigator Brochure (IB).

Sincerely,



John Ferguson, MD  
Vice President  
Drug Safety and Risk Management  
Biogen Idec

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*élan*

**IMPORTANT DRUG WARNING  
VOLUNTARY SUSPENSION OF  
TYSABRI® (natalizumab) MARKETING**

February 28, 2005

Dear Healthcare Professional,

Biogen Idec and Elan Pharmaceuticals are announcing a voluntary suspension in the marketing of TYSABRI, a multiple sclerosis therapy. We are suspending supply of TYSABRI from commercial distribution and physicians should suspend dosing of TYSABRI until further notification. In addition, we have suspended dosing in all clinical trials. These actions, which we believe are in the best interest of patients, have been taken in consultation with FDA. You will be notified regarding the procedure for returning unused product.

This decision is based on reports of two serious adverse events that have occurred in patients treated with TYSABRI in combination with AVONEX® (Interferon beta-1a) in clinical trials of multiple sclerosis. These events involve one fatal, confirmed case and one suspected case of progressive multifocal leukoencephalopathy (PML), a rare and frequently fatal demyelinating disease.

We recommend that you evaluate your patients with signs and symptoms of PML and immediately report any potential case to Biogen Idec at 1-888-489-7227. Alternatively, this information may be reported to FDA's MedWatch reporting system by telephone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch web site at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20853-9787.

Both patients described in these reports received more than 2 years of TYSABRI therapy (37 and 28 monthly doses) in combination with AVONEX. Neither patient had a known history

of immunosuppression. Both patients presented with progressive neurological deterioration, initially suspected to be worsening of pre-existing multiple sclerosis. Due to the progressive nature of the symptoms and MRI findings atypical for multiple sclerosis, alternate diagnoses were sought, leading to consideration of PML.

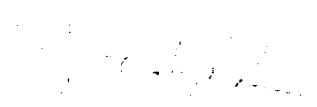
In total, approximately 3,000 patients have been treated with TYSABRI in clinical trials of multiple sclerosis, Crohn's disease, and rheumatoid arthritis. The two cases described above are the only reports of PML to date in multiple sclerosis patients treated with natalizumab and AVONEX combination therapy. To date, we have received no reports of PML in multiple sclerosis patients receiving monotherapy with either TYSABRI or AVONEX, nor have we received any reports of PML in patients with Crohn's disease or rheumatoid arthritis in TYSABRI clinical trials.

PML is a rare, progressive, demyelinating disease of the central nervous system that primarily affects immuno-compromised patients. PML is caused by activation of JC virus, a polyomavirus that resides in latent form in up to 80% of healthy adults. The factors leading to activation of the latent infection are not fully understood.


The presenting symptoms of PML typically include impaired cognition, cortical blindness, and hemiparesis. PML lesions are hyperintense on T2-weighted MRI scans and usually do not enhance on T1-weighted scans following gadolinium infusion, unlike new multiple sclerosis lesions, which usually enhance for up to 2 months. Most PML patients have multifocal lesions of the white matter, although some cases may present with a single new lesion, usually without mass effect.

We are extensively evaluating TYSABRI-treated patients in clinical trials and convening an expert panel to better understand the possible risk of PML in TYSABRI-treated patients. Because we believe in the promising therapeutic benefit of TYSABRI we are working to complete these evaluations quickly. We will use the outcome of these evaluations, in discussion with regulatory authorities, to determine future commercial availability. We will inform you of important new information or developments. If you have further questions or require additional information, please contact Biogen Idec at 1-888-489-7227.

Sincerely,



Burt Adelman, MD  
Executive Vice President,  
Development  
Biogen Idec



Lars Ekman, MD, Ph.D.  
Executive Vice President and President  
Global Research and Development  
Elan Pharmaceuticals

## **EXHIBIT 15**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS  
ADVISORY COMMITTEE

Volume I

Tuesday, March 7, 2006

1:55 p.m.

Holiday Inn Gaithersburg  
The Ballrooms  
2 Montgomery Village Avenue  
Gaithersburg, Maryland

**\*\* EXCERPT ONLY \*\***

**A complete copy of the transcript from the Peripheral and Central Nervous System Drugs Advisory Committee hearings is contained in the Appendix Of The Publicly-Available Complete Transcript Of The March 7-8, 2006, Advisory Committee Hearings, submitted herewith.**

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## Questions from the Committee

345

1 Dr. Michael Panzara, who will present the safety of  
2 natalizumab.

3 Safety Data

4 DR. PANZARA: Good morning, ladies and  
5 gentlemen. I am Dr. Michael Panzara, and I will  
6 review for you today the safety of natalizumab.

7 [Slide.]

8 This slide provides an outline of my  
9 presentation. As has been discussed, natalizumab  
10 was approved in November of 2004 for the treatment  
11 of relapsing forms of multiple sclerosis based on  
12 one-year data from the two ongoing Phase III  
13 studies.

14 The studies are now complete and an  
15 analysis of the safety database has yielded no  
16 appreciable differences in most adverse events as  
17 compared with the time of initial approval.

18 Therefore, I will only briefly review the  
19 general safety of natalizumab. The details of  
20 these analyses are in your briefing document, and I  
21 am pleased to answer any questions that you may  
22 have about them.

1           The one thing that has changed since the  
2   time of initial approval is infection. Therefore,  
3   the bulk of my presentation will focus on a review  
4   of the many analyses undertaken to evaluate the  
5   risk of infection in natalizumab-treated patients.

6           The final portion of my presentation will  
7   focus on progressive multifocal  
8   leukoencephalopathy, or PML, and the extensive  
9   safety evaluations undertaken following  
10  identification of PML in natalizumab-treated  
11  patients.

12           [Slide.]

13           Most of my presentation will focus on the  
14  placebo-controlled MS experience. This included  
15  1,617 patients who received natalizumab and 1,135  
16  who received placebo. There were also patients who  
17  received natalizumab in open-label studies  
18  amounting to over 2,300 MS patients and 3,800  
19  patient years of exposure.

20           I will also call upon the experience in  
21  Crohn's disease in which an additional 1,600  
22  patients received natalizumab, amounting to 1,700

1 person years of exposure, and there were some  
2 differences in the safety profile in this  
3 population, which I will indicate throughout my  
4 presentation.

5 All together, in the combined experience,  
6 nearly 4,000 patients received natalizumab and  
7 5,500 person years of exposure. In addition, there  
8 was a small rheumatoid arthritis experience, which  
9 I will also speak of during my presentation.

10 [Slide.]

11 This slide provides a general overview of  
12 the adverse events that occurred in the  
13 double-blind, placebo-controlled trials of multiple  
14 sclerosis.

15 Focusing on the first line, common adverse  
16 events were balanced between the groups.  
17 Similarly, serious adverse events were balanced,  
18 and, indeed, there were more serious adverse events  
19 on placebo than on natalizumab. This is reflective  
20 of more serious MS relapses in the placebo group as  
21 compared with natalizumab.

22 Moving to the next line, when these

1 serious adverse events are removed, the MS-related  
2 ones, the groups remained balanced.

3           Serious hypersensitivity reactions did  
4 occur on natalizumab treatment at an incidence of  
5 0.8 percent. This is the same incidence that was  
6 seen at the time of initial approval, and, indeed,  
7 there were no serious hypersensitivity reactions  
8 during the second year of the trial.

9           Moving to malignancies, 1.3 percent of  
10 placebo-treated patients had a malignancy versus  
11 0.7 percent of those on natalizumab.

12           There were three deaths on placebo versus  
13 2 on natalizumab. The deaths on natalizumab are  
14 summarized on the next slide.

15           [Slide.]

16           The first patient was a patient who had a  
17 history of malignant melanoma, who noticed a new  
18 lesion at the time of his first or second infusion,  
19 and the diagnosis was finally made after his fifth  
20 infusion.

21           The next was a patient who had received 25  
22 infusions of natalizumab, but died of alcohol



1 intoxication.

2 [Slide.]

3 In addition, there were four deaths that  
4 occurred in the open-label MS experience. The  
5 first was one of the cases of PML that I will  
6 describe in detail for you later in my  
7 presentation.

8 There was one case each of a respiratory  
9 distress in a pediatric MS patient, a patient who  
10 had a seizure and arrhythmia, and one patient  
11 suicide. Each of these last three events occurred  
12 at least five months after their last natalizumab  
13 infusion.

14 [Slide.]

15 Turning to the Crohn's disease experience,  
16 there were six deaths that occurred in Crohn's  
17 disease clinical trials, both the  
18 placebo-controlled trials and the open-label  
19 trials.

20 The first was a patient who died of a  
21 work-related asphyxiation. The second was a  
22 65-year-old man with a history of hypertension who

1 died of a myocardial infarction. The third was a  
2 patient who developed peritonitis as a  
3 postoperative complication of a Crohn's related  
4 procedure.

5           The next three events were serious  
6 opportunistic infections. The first was the one  
7 case of PML in a Crohn's disease patient. The next  
8 was a patient who developed pneumocystis carinii  
9 pneumonia, and the third was a patient who  
10 developed pulmonary aspergillosis. I will describe  
11 each of these last three events in detail during my  
12 discussion of opportunistic infections.

13           [Slide.]

14           Finally, there were two deaths in  
15 natalizumab-treated patients in the rheumatoid  
16 arthritis experience. The first was in a patient  
17 who developed a renal stone and then developed E.  
18 coli urosepsis that in the process of placing a  
19 central line for antibiotic treatment, developed an  
20 intraoperative pulmonary hemorrhage.

21           The final case was a woman with rheumatoid  
22 lung, which was diagnosed on autopsy.

1           So, these slides summarize the total  
2   number of deaths that occurred on natalizumab  
3   treatment in the clinical development program.

4           [Slide.]

5           Now, I would like to turn to a discussion  
6   of infections.

7           [Slide.]

8           I would like to begin by providing an  
9   overview of the many analyses undertaken to  
10   evaluate the risk of infection in  
11   natalizumab-treated patients. This will include a  
12   discussion of common infections, as well as those  
13   reported as serious.

14          Then, I will review the risk of infection  
15   over time, in other words, were there an increasing  
16   number of infections with increasing natalizumab  
17   exposure.

18          Then, I will discuss an analysis of herpes  
19   infections. This is a relatively common viral  
20   infection that we chose to study to evaluate  
21   potential effects of natalizumab on cell-mediated  
22   immunity.

1           Finally, I will review opportunistic  
2   infections including PML.

3           [Slide.]

4           This slide shows the common infections  
5   that occurred in the placebo-controlled trials of  
6   multiple sclerosis, that occurred at an incidence  
7   of 1 percent or greater than placebo on natalizumab  
8   treatment.

9           Focusing on the first line, 74 percent of  
10   patients in each group experienced an infection.  
11   There were five infections that occurred more  
12   frequently on natalizumab than placebo using this  
13   low threshold of 1 percent.

14          The types of infections that developed are  
15   quite typical of those seen in this population.  
16   Similar to the incidence, the rate of infection was  
17   balanced at 1.5 per person year in each group.

18          [Slide.]

19          This slide shows the serious infections  
20   that occurred in the placebo-controlled trials of  
21   multiple sclerosis. The infections on this slide  
22   are those that occurred at an incidence of 0.1

1 percent or greater in the natalizumab group.

2           The most common serious infections were  
3    appendicitis, urinary tract infections, and  
4    pneumonia with a maximal difference between the  
5    groups of 0.1 percent.

6           On the middle of the slide, you can see  
7    there were three reports of what was deemed a  
8    serious viral infection. Each of these were  
9    patients who developed nausea, vomiting, and fever.  
10   The viral infection resolved spontaneously or with  
11   hydration. All patients recovered and continued in  
12   the study.

13           [Slide.]

14           Now, I would like to summarize the  
15   post-marketing natalizumab experience for  
16   infections. Approximately 7,000 patients received  
17   one or more natalizumab infusions in the three  
18   months that the drug was on the U.S. market.

19           Serious infections were reported in 16  
20   patients, yielding reporting incidence of 0.2  
21   percent. Pneumonia and urinary tract infections  
22   were the most common infections reported.

1           There were two reports of serious herpes  
2   infections that occurred in the post-marketing  
3   period. The first was a case of fatal herpes  
4   encephalitis that occurred three months following a  
5   single natalizumab infusion.

6           The second was a case of herpes simplex  
7   meningitis that occurred within hours of a single  
8   natalizumab infusion. This patient recovered fully.

9           There were no opportunistic infections  
10   reported during this time including no reported  
11   cases of PML.

12           [Slide.]

13           Now, turning to the risk of infection over  
14   time. We set out to determine whether with  
15   increasing natalizumab exposure, there would be an  
16   increased risk of infection.

17           This slide is again from the double-blind,  
18   placebo-controlled trials of multiple sclerosis.  
19   The y axis shows the cumulative probability of an  
20   infection, and the x axis shows the number of weeks  
21   in the trial.

22           The Kaplan-Meier curves are nearly

1   superimposable. This indicates an equal risk of  
2   infection over the 120-week dosing interval.  
3   Likewise, the hazard ratio was 1, supporting this  
4   conclusion.

5               Thus, with increasing natalizumab  
6   exposure, there does not appear to be an increased  
7   risk of infection.

8               [Slide.]

9               Now, turning to herpes infections. As I  
10   indicated, we chose to study herpes viral  
11   infections as a marker of potential effects of  
12   natalizumab on cell-mediated immunity.

13              These are latent DNA viruses in which  
14   reactivation leads to the clinical manifestations  
15   of disease, and these viruses have a particular  
16   tropism for the nervous system. The high rate of  
17   sporadic infection in these viruses makes it  
18   amenable to study in the clinical trial setting.

19              [Slide.]

20              This table shows the incidence and rate of  
21   herpes infections that occurred in the  
22   placebo-controlled trials of multiple sclerosis.



1 Infections included in this table are  
2 those reported as herpes simplex, herpes zoster,  
3 cytomegalovirus, Epstein-Barr virus, or any  
4 infection deemed as herpetic by the investigator.

5 7.2 percent of patients on natalizumab  
6 experienced a herpes infection versus 6.1 percent  
7 of those on placebo.

8 We chose to explore this further by  
9 evaluating the incidence and rate of herpetic  
10 infections in the monotherapy study, as well as  
11 those in the combination study, and that is shown  
12 on this slide.

13 [Slide.]

14 First, focusing on the monotherapy, 6  
15 percent of patients on placebo versus 6.4 percent  
16 of those on natalizumab experienced a herpetic  
17 infection, and the rate was also balanced between  
18 the groups.

19 In contrast, in combination therapy, 6.1  
20 percent of those on placebo or Avonex alone  
21 experienced a herpetic infection as opposed to 8.4  
22 percent of those on natalizumab, and this is

1 reflected in the rate of 50 per 1,000 person years  
2 versus 67 per 1,000 person years.

3 So, this suggests that although there may  
4 be an increased risk of herpes infections that are  
5 slight, it appears to be greater in those receiving  
6 combination therapy.

7 So, to summarize, there was a slight  
8 increase in herpes infections of 1.1 percent in  
9 natalizumab-treated patients. It appears that this  
10 occurred primarily with combination treatment.  
11 There are no serious or disseminated herpes  
12 infections in the multiple sclerosis trials. There  
13 were the two cases of herpes infections in the  
14 post-marketing experience that I already described  
15 for you.

16 Although I didn't just show it, it is in  
17 your briefing document that this observation in  
18 Crohn's disease was similar. There was an increase  
19 of 0.5 percent on natalizumab-treated patients as  
20 compared with placebo.

21 Five of these events were reported as  
22 serious in the Crohn's disease trials. Two of the

1 five had onset prior to the initiation of  
2 natalizumab treatment, and all patients recovered  
3 when appropriate treatment was initiated.

4 [Slide.]

5 Now, I would like to turn to a discussion  
6 of opportunistic infections.

7 [Slide.]

8 PML did occur in natalizumab-treated  
9 patients. There were a total of three confirmed  
10 cases of PML. Two of these were in MS patients,  
11 one of these was fatal. Both patients were  
12 receiving interferon-beta concurrently at the time  
13 of diagnosis.

14 There was also one patient with PML in the  
15 Crohn's disease studies which was also fatal. This  
16 patient was originally diagnosed as having an  
17 astrocytoma, but later, a re-review of the  
18 pathology by an independent neuropathologist  
19 determined that the diagnosis was actually PML.  
20 This patient had pre-existing lymphopenia due to  
21 chronic immunosuppression use.

22 The exposure of natalizumab in these

1 patients ranged from 8 to 37 infusions and all of  
2 these patients presented with behavioral changes.

3 [Slide.]

4 This table shows the incidence of  
5 opportunistic infections in the placebo-controlled  
6 experience, as well as the cumulative MS experience  
7 for natalizumab.

8 Focusing on the righthand side of the  
9 slide, in the blue shaded area, there were a total  
10 of three patients who developed opportunistic  
11 infections on natalizumab, yielding a rate of 0.8  
12 per 1,000 person years. Two of these were the  
13 cases of PML that I have just described.

14 The only other opportunistic infection was  
15 a patient who developed a cryptosporidial  
16 gastroenteritis after 16 natalizumab infusions.  
17 This patient recovered fully.

18 Thus, other than PML, there was only one  
19 opportunistic infection in the MS experience.

20 [Slide.]

21 Turning to Crohn's disease, this slide  
22 shows the incidence of opportunistic infections in

1 the placebo-controlled and cumulative experience in  
2 Crohn's disease.

3 Again, focusing on the righthand portion  
4 of the slide, there were five events that were  
5 characterized as opportunistic in patients in the  
6 Crohn's disease studies, yielding a rate of 2.9 per  
7 1,000 person years. The details of these cases are  
8 shown in the next slide.

9 [Slide.]

10 Starting at the top of the slide, the  
11 first was the one PML case that I have already  
12 described. The next two cases I have mentioned  
13 when I reviewed the deaths on the natalizumab  
14 treatment.

15 The first was a 69-year-old man who  
16 developed pneumocystis carinii pneumonia following  
17 34 natalizumab infusions in the setting of chronic  
18 cirrhosis.

19 The next patient was a 63-year-old man who  
20 developed pulmonary aspergillosis after a prolonged  
21 hospitalization that resulted from a GI bleed in  
22 the setting of chronic prednisolone and

1 nonsteroidal use.

2           The next patient is a 33-year-old woman  
3 who developed CMV colitis following a single  
4 natalizumab infusion in the setting of  
5 azathioprine. This patient recovered  
6 spontaneously.

7           The final case was a 65-year-old woman who  
8 developed a mycobacterium avium intracellulare  
9 pneumonia following eight natalizumab infusions in  
10 the setting of chronic prednisone use, in the  
11 setting of staph aureus pneumonia. This patient  
12 also recovered fully with treatment.

13           The next three events on the slide are not  
14 considered opportunistic, but are somewhat atypical  
15 and are considered for completeness.

16           The first is a 32-year-old man who  
17 developed a lung abscess following 13 infusions of  
18 natalizumab in the setting of azathioprine. This  
19 patient recovered fully with antibiotic treatment.

20           The next is a 62-year-old woman who  
21 developed Burkholderia cepacia pneumonia, also  
22 known as pseudomonas cepacia pneumonia, following

1 three natalizumab infusions in the setting of  
2 tobacco use and congestive heart failure. This  
3 patient also recovered fully.

4 Finally, there is a 20-year-old man who  
5 developed what is presumed to be tuberculosis  
6 following 25 natalizumab infusions in the setting  
7 of prednisone and azathioprine use. This developed  
8 six months following his last natalizumab infusion.  
9 Although the diagnosis has not been confirmed  
10 either by PCR or by culture, the patient remains on  
11 tuberculosis treatment.

12 [Slide.]

13 So, to summarize, natalizumab treatment is  
14 associated with an increased risk of PML. The  
15 incidence estimate is 1 in 1,000 with broad  
16 confidence intervals ranging from 0.2 per 1,000 to  
17 2.8 per 1,000.

18 There may also be an increased risk of  
19 other opportunistic infections. There was one  
20 non-PML infection in MS patients. This is the  
21 cryptosporidial diarrhea.

22 The remaining infections occurred in



1 Crohn's disease patient with pre-existing  
2 comorbidity and immunocompromise. This may be  
3 reflective of any of these factors, and, indeed,  
4 there was a slight increase in infection in general  
5 in Crohn's disease patients.

6 [Slide.]

7 So, to summarize the safety of  
8 natalizumab, adverse events and serious adverse  
9 events were balanced between the groups. The  
10 hypersensitivity rate of 0.8 percent was consistent  
11 with the approved labeling and there was no  
12 increase in malignancy on natalizumab treatment.

13 There was no increase in the incidence or  
14 rate of common or serious infections.

15 There may be a slight increase in herpes  
16 infections on natalizumab treatment, and this  
17 appears to be more prevalent in the combination  
18 patients.

19 PML and other opportunistic infections did  
20 occur on natalizumab treatment, and these were seen  
21 mostly in Crohn's disease patients with significant  
22 comorbidity or the use of immunomodulators or

1 immunosuppressants.

2 [Slide.]

3 Now, I would like to summarize PML.

4 [Slide.]

5 First, PML is a rare, progressive  
6 infection of the central nervous system. It is  
7 often fatal within six months of diagnosis.

8 It is a lytic infection of  
9 oligodendrocytes caused by the JC virus, which is a  
10 human polyomavirus.

11 It is known to primarily affect  
12 immunocompromised individuals and was first  
13 described in the setting of hematological  
14 malignancies. It gained more prominence during the  
15 era of HIV infections, and most recently it has  
16 been described in the setting of organ  
17 transplantation.

18 [Slide.]

19 The cause of PML is the JC virus. This is  
20 a double-stranded DNA virus that is believed to  
21 infect the majority of individuals at an early age.  
22 However, the reported seroprevalence ranges from 30

1 to 80 percent depending on the assays employed.

2 The sites of latency of the JC virus  
3 include the kidney, the bone marrow, and lymphoid  
4 tissues.

5 The pathogenesis of PML is really not  
6 known, however, it likely involves a multi-step  
7 process that involves the activation of the virus  
8 from latency, a step of DNA rearrangement,  
9 interactions with the immune system, and eventual  
10 migration of the virus from sites of latency into  
11 the central nervous system.

12 [Slide.]

13 The diagnosis of PML is based on a triad  
14 of clinical, MRI, and laboratory findings. First,  
15 clinically, it is characterized by a subacute onset  
16 of progressive neurological changes. The symptoms  
17 typically localize to the subcortical region, but  
18 may also involve cerebellum.

19 On MRI, the lesions are T2-hyperintense  
20 and are typically non-enhancing without mass  
21 effect, and typically localized to the subcortical  
22 region as do the symptoms.

1           Diagnosis requires confirmation of the  
2   presence of JC virus in the central nervous system,  
3   and this is done commonly now through the use of  
4   PCR analysis of the spinal fluid looking for DNA  
5   from the JC virus.

6           Although there are no pathognomonic  
7   differences for multiple sclerosis, there are  
8   features that help one differentiate between the  
9   two.

10          First, in terms of the clinical  
11   presentation, the tempo is different. While PML  
12   symptoms typically are subacute, those of MS are  
13   typically more acute, evolving over hours to days.  
14   Likewise, the location of the lesions are somewhat  
15   different.

16          MS typically affects optic nerve or spinal  
17   cord, although can affect other areas, while these  
18   areas are almost never involved in the setting of  
19   PML, particularly the optic nerve and spinal cord.

20          On MRI, although T2 lesions develop in MS,  
21   they are typically associated with  
22   gadolinium-enhancement, edema or mass effect, and

1 are more typically periventricular.

2 In addition, JC viral DNA is not detected  
3 in the spinal fluid of MS patients.

4 There are currently no proven means for  
5 monitoring or predicting PML onset. A variety of  
6 methods have been explored. This includes serum,  
7 plasma, buffy coat, in white cells and urine. None  
8 of these have proven to be predictive or  
9 diagnostic.

10 [Slide.]

11 Unfortunately, there are no antiviral  
12 treatments for PML. It appears based on the  
13 literature that immune reconstitution may be the  
14 most effective treatment.

15 This comes from two lines of evidence.  
16 First, is the HIV experience with highly active  
17 antiretroviral treatments, or HAART. The  
18 literature shows that the introduction of HAART, at  
19 the time of diagnosis reduces the mortality of PML  
20 by half.

21 In addition, this literature has suggested  
22 that mild symptoms at treatment initiation, so

1 early in the disease, is associated with an  
2 improved prognosis.

3 The second line of evidence stems from  
4 transplantation. This literature has suggested  
5 that a reduction of immunosuppression at the time  
6 of clinical presentation of PML can improve  
7 survival, and survival is reported in one-third of  
8 patients in case series, although the experience is  
9 small.

10 The data suggest that early recognition  
11 and immune reconstitution may improve outcome.

12 [Slide.]

13 Now, I would like to review the extensive  
14 safety evaluations undertaken following  
15 identification of PML in natalizumab-treated  
16 patients.

17 [Slide.]

18 Following the suspension of dosing on the  
19 28th of February, we evaluated the patients from  
20 the clinical trials of multiple sclerosis, Crohn's  
21 disease, and rheumatoid arthritis.

22 The objectives of these evaluations were

1 3-fold. First, to determine if additional patients  
2 had undiagnosed PML or other atypical infections.  
3 Next, to determine the true prevalence of JC viral  
4 DNA in the CSF of MS patients. There was a small  
5 literature that said that JC viral DNA can be  
6 detected in up to 10 percent of MS patients. We  
7 set out to determine if this was correct.

8 Finally, we set out to assess the utility  
9 of plasma testing as a predictive test for PML.

10 [Slide.]

11 All patients were required to see their  
12 neurologist as soon as possible following dose  
13 suspension for a clinical evaluation and MRI.

14 We encouraged CSF collection for all  
15 patients, but it was required for anyone for which  
16 there was suspicion of PML.

17 We also collected plasma for exploratory  
18 analyses, and we are fortunate to have CSF and  
19 plasma control samples from the Karolinska  
20 Institute. These were from patients who were naive  
21 to treatment and those who had other neurological  
22 diseases.



1           The entire study was done in collaboration  
2   with the NIH and was monitored by an independent  
3   Adjudication Committee of experts in virology,  
4   neuroradiology, and the neurology of HIV. The role  
5   of this committee was to determine whether there  
6   are new cases of PML.

7           [Slide.]

8           Now, to the results.

9           [Slide.]

10          3,826 patients were eligible for  
11   evaluation. Ninety-one percent of the  
12   natalizumab-treated patients participated in this  
13   assessment. We had very extensive follow-up even  
14   on those who did not participate, and vital status  
15   was confirmed in over 99 percent.

16          Following this detailed analysis, there  
17   were no new cases of PML.

18          [Slide.]

19          Now, in addition to determining there were  
20   no cases of PML, we learned a great deal about PML  
21   diagnosis and monitoring.

22          First, regarding MRI, we had approximately

1 3,000 MRI scans that were reviewed by our central  
2 reader centers. We found that MRI scan was very  
3 useful to exclude the diagnosis of PML in the  
4 setting of clinical change, in the setting of  
5 patients with clinical symptoms.

6 We found that a single MRI scan was  
7 usually sufficient to rule out the diagnosis,  
8 although if there were ambiguous lesions, re-scan  
9 was sometimes required.

10 When the MRI was nondiagnostic, spinal  
11 fluid analysis was required. We found during this  
12 analysis that baseline brain MRI was very important  
13 to facilitate this assessment.

14 [Slide.]

15 We analyzed nearly 800 spinal fluid  
16 samples for the presence of JC viral DNA; 400 of  
17 these were from natalizumab-treated patients. An  
18 additional 400 were the neurological controls from  
19 the Karolinska Institute.

20 Following these analyses, no JC viral DNA  
21 was detected in either natalizumab-treated patients  
22 and those who had never seen the drug.

1           We also had spinal fluid samples from the  
2 two MS patients who had developed PML, and JC virus  
3 was detected in the spinal fluid of those two  
4 patients. Thus, this data confirms that CSF  
5 testing is very specific for the diagnosis of PML.

6           [Slide.]

7           Finally, turning to the plasma analyses,  
8 plasma was collected from 2,370 patients as an  
9 exploratory analysis. Five of these patients were  
10 found to have detectable JC viral DNA in their  
11 plasma, or 0.2 percent.

12           There were no clinical or radiographical  
13 changes associated with this finding, and, indeed,  
14 three of these patients had never received  
15 natalizumab.

16           We also re-analyzed stored serum samples  
17 from the three PML patients. JC viral DNA was not  
18 detected in two of three of these prior to symptom  
19 onset. The one patient with Crohn's disease had JC  
20 virus detected about a month before clinical  
21 symptoms.

22           So, this suggests the presence of JC virus

1 or viremia is not necessarily associated with PML,  
2 but the absence of JC virus does not exclude the  
3 diagnosis.

4 [Slide.]

5 So, in closing, although there are no  
6 proven ways to monitor for PML, there are a few  
7 options that we can consider. These options extend  
8 from the extensive evaluations over the past year,  
9 opinions from consultants, and the existing  
10 literature.

11 We believe that clinical vigilance by the  
12 neurologists is the most important means of  
13 screening. In addition, we believe that the  
14 monthly interaction between healthcare provider and  
15 patients at the time of infusion affords a unique  
16 opportunity to enhance this vigilance through the  
17 introduction of questionnaires or checklists that  
18 have a sufficiently low threshold to prompt  
19 additional evaluations by the physician.

20 The three patients who developed PML in  
21 our experience each presented with clinical signs  
22 early in the course of the disease that were

1 recognized by the patient, physician, or family  
2 members.

3 Previously, such changes would have been  
4 viewed changes secondary to multiple sclerosis  
5 rather than a rare disease like PML. Now, with  
6 what we know, any clinical change on natalizumab  
7 will be viewed as PML until proven otherwise,  
8 prompting a rapid dose suspension and additional  
9 assessments.

10 Turning to JC viral DNA in the plasma, we  
11 were hopeful about this, however, the sensitivity  
12 and predictive value appear to be unclear. Given  
13 the presence of virus in patients without PML, and  
14 the lack of patients with PML, what the results of  
15 this test suggest are not clear. Therefore, we do  
16 not believe we can recommend widescale use at this  
17 time.

18 Regarding MRI, we found MRI to be quite  
19 sensitive in the setting of new changes, but not  
20 specific in MS, but helpful diagnostically.  
21 However, given the time course of PML, which is  
22 relatively short, we could think of no practical

1 scanning frequency which would allow its use as an  
2 effective screening tool.

3 Finally, regarding spinal fluid, we found  
4 spinal fluid to be very specific at the time of  
5 diagnosis, however, the literature suggests that  
6 spinal fluid tends to be negative in early disease,  
7 even in the setting of clinical changes in MRI.  
8 This, and the fact that this is an invasive test,  
9 make it a poor screening tool.

10 So, these are the factors that we  
11 considered when designing the risk management plan  
12 that Dr. Bozic will now present to you.

13 Thank you.

14 DR. KIEBURTZ: Any questions,  
15 clarifications from the committee? Dr. McArthur.

16 DR. McARTHUR: Thank you for your  
17 presentation.

18 I had a question about the performance  
19 characteristics of the spinal fluid JCV-PCR. You  
20 have talked about the very low rate, well, the zero  
21 rate of positivity. What about positive controls  
22 from biopsy-proven PML cases, either HIV-positive

1 or not?

2 DR. PANZARA: These assays were run at the  
3 NIH using a Gene Majors method, which has a  
4 detection of 50 nanograms or 50 copies, I should  
5 say, per ml. So, it was the most sensitive assay  
6 available, and positive controls were used.  
7 Indeed, it was the same assay in which we detected  
8 JC virus in the spinal fluid of the confirmed  
9 cases.

10 DR. McARTHUR: Were the positive controls  
11 re-run in this assay, or were they essentially  
12 historical controls?

13 DR. PANZARA: No, they were positive  
14 controls run at the time of the assay, at the time  
15 of testing of these samples.

16 DR. KIEBURTZ: Dr. Jung.

17 DR. JUNG: I have a number of questions.

18 DR. KIEBURTZ: Just now clarifications,  
19 misunderstandings, misheards. General questions,  
20 we will get to. I just don't want to interrupt the  
21 sponsor too much.

22 DR. JUNG: Headaches were mentioned as



1 occurring in 35 percent of patients receiving  
2 Tysabri as opposed to 30 percent. Was there any  
3 concern that the presentation of headaches might  
4 serve as a precursor for HSV?

5 DR. PANZARA: Headache was the most common  
6 infusion-related reaction. We characterized any  
7 event that occurred within two hours of infusion as  
8 an infusion reaction. Headache was the most common  
9 event reported. It was usually reported early in  
10 the course of treatment, and then decreased over  
11 time, but it was no precursor to an infection. The  
12 patients, the vast majority continued in the trial.

13 DR. RICAURTE: Just following up on the  
14 issue of spinal fluid, did you address the question  
15 about high specificity in that sensitivity may be  
16 compromised particularly early on? I wondered if  
17 you could say a few more words about the extent of  
18 that and how that might or might not have  
19 influenced the evaluation of all of the cases for  
20 possible PML.

21 DR. PANZARA: So, there is a sensitivity  
22 of the spinal fluid. Well, the levels of DNA that

1 are detectable by this method, according to all our  
2 experts, is that which would be considered  
3 clinically relevant. Indeed, there was nothing  
4 detected below this very low threshold. So, we are  
5 very confident that this assay, if there was JC  
6 virus there, we would detect it.

7 DR. KIEBURTZ: Can I ask one last  
8 question? When you were on your slide about  
9 clinical, my attention lapsed for a moment when you  
10 said under clinical vigilance, if there is any  
11 clinical deterioration--what did you say?

12 DR. PANZARA: So, currently, our  
13 recommendation is clinical vigilance, and the risk  
14 management program that Dr. Bozic will describe, we  
15 will go through the steps that should be taken  
16 following the identification of clinical change,  
17 but basically, any clinical change should prompt an  
18 evaluation by a physician and which may include  
19 additional workup.

20 DR. KIEBURTZ: Thanks.

21 Dr. Katz.

22 DR. KATZ: I had a question for Dr.

1 Sandrock and I think a question or two for Dr.

2 Panzara, if that's okay.

3           The first question has to do with the  
4 efficacy data. You presented the data for relapse  
5 rate or annualized relapse rate by baseline EDSS.  
6 Do you have a presentation of the accumulation of  
7 disability results by baseline EDSS as opposed to  
8 just the relapse rate outcome?

9           DR. SANDROCK: Yes, I believe it's 2-9,  
10 display 2-9 in the briefing document that we  
11 provided. That provides the hazard ratio on  
12 subgroups and it is broken down in the same levels  
13 that we broke them down for the relapse rate ratio,  
14 2-10, in fact.

15           May I have Slide 2-16, please. Actually,  
16 could I have displayed 2-10.

17           [Slide.]

18           So, this is the hazard ratio in the  
19 various subgroups. In the third set, there are the  
20 hazard ratios based on the EDSS level zero to 1.5,  
21 2 to 2.5, 3 to 3.5, and greater than and equal to  
22 4.

1 DR. KIEBURTZ: You had some follow-up?

2 DR. KATZ: Yes. For either one who has  
3 the exposure data, what is the exposure, or do you  
4 have a slide for the exposure? I think you had  
5 total person years and that sort of thing, but the  
6 exposure for two years and three years, how many MS  
7 patients have gotten the drug for two years, how  
8 many have gotten it for three years?

9 DR. PANZARA: I would direct you to  
10 display 3-1 in your briefing document, but I do  
11 have a slide of that. That would be Slide 2-18.

12 [Slide.]

13 I direct your attention to the top portion  
14 of the table where we have number exposed to  
15 natalizumab. I would like you to focus your  
16 attention to the righthand side of the slide where  
17 you can see approximately 1,400 patients have  
18 received natalizumab for two or more years,  
19 approximately 150 patients have received  
20 natalizumab for three or more years. The bulk of  
21 that was in multiple sclerosis.

22 DR. KATZ: So, in MS, 1,100 patients--

1 DR. PANZARA: 1,121.

2 DR. KATZ: Exposed for two years.

3 DR. PANZARA: Two years, and 111 for three  
4 or more years.

5 DR. KATZ: Okay. And the two cases of PML  
6 occurred at two years or greater?

7 DR. PANZARA: Yes, one patient had  
8 received 29 natalizumab infusions, and one had  
9 received 37.

10 DR. KATZ: The other question I had, had  
11 to do with vital status. You said that you had  
12 vital status for greater than 99 percent of the  
13 patients, even though 91 percent participated in  
14 the follow-up study.

15 Could you just talk a little bit more  
16 about that? What do you mean by "vital status,"  
17 just alive or dead, or do you have cause of death,  
18 if there were deaths?

19 DR. PANZARA: There were no deaths. The  
20 deaths that I described to you initially in my  
21 presentation are some of those patients, you know,  
22 they weren't eligible clearly. So, we had a total

1 of about 437 patients who chose not to participate  
2 or did not participate in the assessment.

3           There were a variety of reasons for that.  
4 The most common reason was most had received  
5 placebo. We had a large number of patients who  
6 received placebo, had never received natalizumab,  
7 and really didn't feel the need to come in and have  
8 this assessment.

9           We had about another third of the patients  
10 actively decline participation, so they had to sign  
11 that they didn't want to participate, so their  
12 vital status was confirmed. A variety of other  
13 sites, who didn't want to participate, but the  
14 physician said no PML here, but I am not  
15 participating, so there were several of those.

16           There were a few cases, about 60 who were  
17 considered as quote, unquote, "lost to follow-up."  
18 We actually went to each of their physicians and  
19 had those physicians make contact with them, and we  
20 found all patients except for 10.

21           DR. KIEBURTZ: Dr. Couch.

22           DR. COUCH: Yes, just one question about

1 the MRI scan. The MRI scan is obviously one of the  
2 good ways of trying to confirm the diagnosis.

3 Is this an appropriate way of trying to  
4 look for early diagnosis through your IAC? Were  
5 you able to find that there were any ways in using  
6 the MRI scan to try to determine early diagnosis,  
7 so the immune system could be reconstituted early?

8 DR. PANZARA: The requirement was that  
9 everybody undergo an MRI scan, and what we found is  
10 that if there was any patient who had clinical  
11 symptoms that the physician was unsure of, that  
12 could be MS, could be PML, they had the MRI scan  
13 done. They referred both the MRI scan and the  
14 clinical exam to our independent Adjudication  
15 Committee.

16 The expert neuroradiologist on that  
17 committee and clinicians reviewed the history, and  
18 then made recommendation. In some cases, if the  
19 MRI was ambiguous, to go on to an additional MRI,  
20 approximately one to two months later, or a spinal  
21 tap. That was the diagnostic algorithm.

22 So, if there was any concern, they



1 underwent, first, MRI. If there was still concern,  
2 additional MRI and spinal tap was performed. We  
3 saw no signs on the scans that were reviewed. We  
4 were actively looking for the immune reconstitution  
5 syndrome, and we did not see any scans that would  
6 be suggestive of that.

7 DR. KIEBURTZ: I know the committee has  
8 further questions, but I am going to hold and let  
9 the sponsor finish their presentations, please, and  
10 we will credit you five minutes for our intervening  
11 questions.

12 Risk Management Plan

13 DR. BOZIC: Good morning, ladies and  
14 gentlemen. My name is Carmen Bozic and I am the  
15 head of Drug Safety and Risk Management at Biogen  
16 Idec.

17 So far this morning, you have heard this  
18 Dr. Sandrock and Dr. Panzara present on the  
19 efficacy and safety of natalizumab. In this  
20 presentation, I will focus on how we propose to  
21 minimize the risk of PML and also what we plan to  
22 do in order to better understand that risk.

1 [Slide.]

2 This is an outline of my presentation.

3 After I conclude with the risk management plan, I  
4 will present our perspectives on the benefit-risk  
5 profile of Tysabri.

6 [Slide.]

7 So, the Tysabri risk management plan was  
8 developed based on FDA's guidance document on this  
9 topic and based on our ongoing dialogue with the  
10 FDA.

11 I would like to point out that the plan  
12 that I will be presenting you today is an updated  
13 version of the plan that you have in your briefing  
14 document and represents an evolution in our  
15 thinking and in consideration of several  
16 discussions that we have had with the FDA on this  
17 topic.

18 In developing this plan, we carefully  
19 reviewed other existing risk management plans to  
20 gain insights into the best approach for Tysabri.

21 We found that the approach to risk  
22 management for drugs with serious risks can vary.

1 or another.

2 Let me go back. I missed the most  
3 important slide, my acknowledgment slide. I  
4 apologize to my colleagues. The review team is a  
5 very large team, and if I listed every person on  
6 the review team, I would have to pass out  
7 binoculars to the committee.

8 Our next speaker is Dr. Hughes, and she is  
9 going to talk to you about safety.

10 Safety

11 DR. A. HUGHES: Hi. Thank you very much.

12 [Slide.]

13 In this talk, I am going to discuss our  
14 view of the major safety concerns associated with  
15 natalizumab outside of PML. My goal is to allow  
16 you to consider natalizumab's risk-benefit profile  
17 more fully as you consider the questions that we  
18 have posed to you.

19 [Slide.]

20 I will focus here on just three major  
21 safety issues. First, infections, again, my  
22 discussion is limited entirely to infections other

1 than PML. Second, immunogenicity and  
2 hypersensitivity reactions, which Dr. McDermott has  
3 talked a little bit about in her presentation.  
4 Third, carcinogenicity.

5 My focus on these three concerns is driven  
6 both by the serious adverse events that were  
7 observed in the clinical trial development program,  
8 as well as by theoretical concerns based on  
9 natalizumab's mechanism of action. There is, of  
10 course, an overlap between these two things, but  
11 not a complete overlap.

12 In addition to discussing these three  
13 major safety issues in the context of the  
14 natalizumab clinical trial program, I will, if time  
15 allows, briefly review serious adverse events that  
16 were reported in the brief post-marketing interval.

17 [Slide.]

18 So, the first issue that I am going to  
19 talk about is infections, and just as natalizumab  
20 blocks the migration of leukocytes to sites of  
21 inflammation in the central nervous system, it may  
22 also impair the recruitment of lymphocytes and

1 monocytes to sites of infection.

2           You have heard a lot already about  
3 natalizumab and infections from the sponsor. I  
4 will present data regarding infections in a  
5 slightly different way than you saw it presented in  
6 Dr. Panzara's presentation, that I think is also  
7 useful to consider.

8           In clinical trial, cases that appear to  
9 represent the same type of infection were often  
10 categorized under numerous umbrella terms, and  
11 these distinctions were often helpful, but  
12 sometimes probably not clinically meaningful.

13           For example, an upper respiratory tract  
14 infection might be classified as upper respiratory  
15 tract infection not otherwise specified,  
16 nasopharyngitis, or pharyngitis viral not otherwise  
17 specified, to name just a few of the many terms  
18 denoting upper respiratory tract infections.

19           So, I will consider cases of upper  
20 respiratory tract infections together, as well as  
21 cases of all lower respiratory tract infections  
22 together, as well as all cases of gastroenteritis

1 and vaginal infections to give you a better  
2 understanding, I hope, of the incidences of these  
3 infections.

4 So, after this long preamble, in  
5 placebo-controlled multiple sclerosis studies,  
6 natalizumab and placebo-treated patients had  
7 similar incidences of infections overall and  
8 serious infections.

9 Incidences of upper respiratory tract  
10 infections, which I just talked a lot about, were  
11 similar, as you can see. Incidences of urinary  
12 tract infections, both overall and serious, were  
13 similar in natalizumab and placebo-treated  
14 patients, and this is a safety concern with data  
15 through one year, but it wasn't borne out with the  
16 two-year data.

17 Incidences of gastroenteritis were  
18 similar. That was another concern based on data  
19 just through one year.

20 [Slide.]

21 Infections in which there was a slightly  
22 greater degree of difference between natalizumab

1 and placebo-treated patients in incidence, as you  
2 can see on this slide, were all lower respiratory  
3 tract infections, 13.3 percent of  
4 natalizumab-treated patients had infections  
5 categorized as any type of lower respiratory tract  
6 infections, compared to 12.2 percent of  
7 placebo-treated patients.

8 0.4 percent of patients treated with  
9 natalizumab had serious pneumonias, and this is  
10 compared to 0.2 percent of placebo-treated  
11 patients.

12 I would like to point out again that  
13 natalizumab-treated patients had a slightly higher  
14 incidence of herpes infections compared to  
15 placebo-treated patients, 7 percent compared to  
16 about 6 percent.

17 In terms of atypical infections--and I use  
18 this term on purpose rather than opportunistic  
19 infections--there was one case of cryptosporidial  
20 gastroenteritis in the monotherapy Study 1801.

21 This case is interesting in that  
22 cryptosporidial gastroenteritis can occur in



1 immunocompetent patients, but usually resolved in a  
2 couple of weeks without treatment. This patient,  
3 who was otherwise healthy, 31 years old, again not  
4 on concomitant Avonex, developed diarrhea after the  
5 17th natalizumab infusion, and it didn't resolve  
6 for about 70 days.

7           There was also an acute CMV infection with  
8 transaminitis in the open-label Study 1808. This,  
9 though, is a typical presentation of an acute CMV  
10 infection in an immunocompetent patient.

11           [Slide.]

12           Turning to Crohn's disease studies, there  
13 was a similar incidence of serious infections in  
14 placebo-controlled Crohn's disease studies, 2.5  
15 percent versus 2.6 percent, but there was a  
16 slightly increased incidence of infections overall  
17 in the natalizumab-treated patients compared to the  
18 placebo-treated patients, as you can see, 40  
19 percent versus 36 percent.

20           As listed, the incidences of selected  
21 infections on this slide, you can see that in the  
22 Crohn's disease studies, there was an increased

1 incidence of upper respiratory tract infections,  
2 but not lower respiratory tract infections in  
3 natalizumab-treated patients.

4           On this slide, I would like to note that  
5 herpes infections occurred in 1.6 percent of  
6 natalizumab-treated patients compared to 1 percent  
7 of placebo-treated patients.

8           I should point out here that the  
9 placebo-controlled Crohn's disease studies were  
10 much shorter. Patients received from just 1 to 3  
11 natalizumab infusions.

12           There were two cases of serious viral  
13 meningitis in natalizumab-treated patients in these  
14 short-term, acute treatment, placebo-controlled  
15 Crohn's disease trials, no cases in the  
16 placebo-treated group.

17           These cases were fairly typical for viral  
18 meningitis although they were serious adverse  
19 events and the patients were hospitalized.

20           There were two serious UTIs in  
21 natalizumab-treated patients, none in  
22 placebo-treated patients in the placebo-controlled

1 Crohn's disease studies. Again, this is  
2 considering all UTIs together.

3 In the short-term, placebo-controlled  
4 Crohn's disease studies, there was one serious CMV  
5 infection, a case of CMV colitis. The patient was  
6 also receiving azathioprine.

7 [Slide.]

8 In long-term Crohn's disease studies, that  
9 is where we saw the atypical infections, as the  
10 sponsor noted. There were six serious atypical  
11 lower respiratory tract infections, and I call  
12 these infections atypical either because of the  
13 passage it involved or because of the features of  
14 the case, such as the pneumonia with lung abscess,  
15 a pathogen was never identified in that case.

16 There was a case of pulmonary  
17 aspergillosis, a case of pneumocystis pneumonia, a  
18 case of varicella pneumonia, a case of  
19 mycobacterium avium intracellulare complex  
20 pneumonia, and a case of Burkholderia cepacia  
21 infection, which is a concern in cystic fibrosis  
22 patients, generally not seen or very, very rarely

1 seen in immunocompetent patients.

2 I should mention that of these six cases,  
3 two of the patients were not on any  
4 immunosuppressive medications or any other  
5 immunomodulatory medications. The rest of the  
6 patients, though, were on corticosteroids or  
7 azathioprine, or a combination of those two.

8 I would also like to note that these  
9 infections occurred after varying numbers of  
10 natalizumab infusions, ranging from 3 to 34, and  
11 there was not a clear relationship between the  
12 number of natalizumab infusions and the risk for  
13 atypical infections although that is certainly  
14 based on a very small number of cases or infections  
15 overall, as the sponsor pointed out.

16 There was a case of possible tuberculosis  
17 infection, which you heard about. This is an  
18 interesting case, and based on the information that  
19 we have, I don't think is terribly compelling for  
20 being a TB infection, although it is certainly  
21 concerning with a product like natalizumab.

22 It was a patient who after receiving 22

1 infusions, two and a half months later--and I  
2 should note he had a history of multiple prednisone  
3 courses, and was also taking azathioprine and had  
4 been on that drug for a year and a half--about two  
5 and a half months after 22 natalizumab infusions,  
6 he had surgery for Crohn's disease flare.

7           A couple of months later, he had an  
8 ileostomy takedown, and at that time it was noted  
9 that his peritoneum was studded with granulomas,  
10 and the pathology revealed granulomatous  
11 inflammation with confluent caseous necrosis, and,  
12 of course, Crohn's disease is associated with  
13 non-caseating granulomas, so it was thought to be  
14 representative of a tuberculosis infection, but AFB  
15 staining and PCR testing for mycobacterial DNA were  
16 negative.

17           [Slide.]

18           In terms of immunogenicity, which is the  
19 second major safety concern that I am going to turn  
20 to, treatment with therapeutic proteins can lead to  
21 the formation of antibodies against the product,  
22 and that is why we considered this as a major

1 safety concern, and why the sponsor monitored  
2 anti-natalizumab antibody formation every 12 weeks  
3 in the Phase III multiple sclerosis studies and in  
4 selected Crohn's disease studies, as well.

5 Ten percent of patients had a positive  
6 antibody titer at least once. I should mention  
7 that anti-natalizumab antibody formation is of  
8 great interest because it is associated with  
9 potentially hypersensitivity reactions, decreased  
10 efficacy, and potentially other adverse events.

11 So, getting back to the incidence  
12 formation, 10 percent of patients has a positive  
13 antibody titer at least once. As Dr. McDermott  
14 mentioned, 6 percent of those patients were  
15 persistently positive, so they had at least two  
16 positive antibody titers.

17 Four percent of patients were transiently  
18 positive meaning they were positive once, or they  
19 were positive on their last assessment.

20 The incidence of anti-natalizumab antibody  
21 formation was higher in Study 1802. It was 12  
22 percent compared to Study 1801, and it was 9

1 percent. Actually, I take back what I just said.  
2 The patients who were positive on their last  
3 assessment and weren't followed up again, I believe  
4 those patients were characterized as being  
5 persistently positive.

6 Now, there is a concern, a historical  
7 concern with therapeutic proteins that  
8 intermittent, irregular infusions may lead to a  
9 higher incidence of antibody formation against the  
10 product. We don't have enough information from the  
11 natalizumab trials about whether intermittent,  
12 irregular infusions, so not monthly, could lead to  
13 a higher incidence of antibody formation than was  
14 seen generally, about 10 percent.

15 These was a study, Study 251, a Crohn's  
16 disease study, in which patients were dosed when  
17 they had flares, and that study has the potential  
18 to give us some information about this issue, but  
19 the numbers are really too small to draw any  
20 conclusions about them.

21 [Slide.]

22 Anti-natalizumab antibody formation was



1 strongly associated with infusion reactions and  
2 hypersensitivity reactions.

3 Infusion reactions occurred in 77 percent  
4 of persistently antibody-positive patients. Again,  
5 infusion reactions were defined as adverse events  
6 that occurred within two hours of the start of the  
7 natalizumab infusion.

8 So, they occurred in 77 percent of  
9 persistently positive antibody-positive patients  
10 compared to 20 percent of antibody-negative  
11 patients and 29 percent of transiently  
12 antibody-positive patients.

13 So, the profile of the transiently  
14 positive patients was actually very close to the  
15 profile of the antibody-negative patients. It was  
16 really the persistently antibody-positive patients  
17 that stood out in terms of the infusion reactions  
18 and the increased multiple sclerosis relapses,  
19 which I will talk about in the next slide.

20 Anaphylactic reactions very notably  
21 occurred in 5.3 percent of antibody-positive  
22 patients in the Studies 1801 and 1802, in which

1 anti-natalizumab antibody formation was assessed,  
2 and it occurred in no patients who were  
3 antibody-negative throughout these studies.

4 In the Crohn's disease studies, which  
5 again were much shorter, anaphylactic reactions  
6 occurred in 1.3 percent of antibody-positive  
7 patients, and again in no antibody-negative  
8 patients.

9 [Slide.]

10 Multiple sclerosis relapses and also  
11 Crohn's disease exacerbations were reported more  
12 frequently as adverse events in antibody-positive  
13 patients compared both to transiently positive  
14 patients and antibody-negative patients.

15 Again, this is just adverse events that  
16 were reported, not relapse defined by any  
17 meaningful criteria. Fifty-seven percent of  
18 antibody-positive patients had adverse events of  
19 multiple sclerosis relapse compared to 35 percent  
20 of antibody-negative patients.

21 The incidence of infections,  
22 interestingly, was lower in persistently

1 antibody-positive patients compared to  
2 antibody-negative patients.

3 Overall, infections were reported in 69  
4 percent of persistently antibody-positive patients  
5 compared to 82 percent of antibody-negative  
6 patients. This pattern was seen for many of the  
7 individual infections, as well.

8 Just to select herpes infections, which  
9 are of concern to us, they were observed--and this  
10 is simplex and zoster, all herpes infections--they  
11 were observed in 2.7 percent of persistently  
12 antibody-positive patients compared to 8.4 percent  
13 of antibody-negative patients, and this is in the  
14 two pivotal studies, 1801 and 1802.

15 [Slide.]

16 Just briefly to talk about the overall  
17 population of patients, again not getting away from  
18 antibody-positive versus antibody-negative  
19 patients, anaphylactic reactions were observed in  
20 multiple sclerosis placebo-controlled studies in  
21 0.4 percent of patients treated with natalizumab  
22 compared to 0.2 percent of patients treated with

1 placebo.

2 In the shorter Crohn's disease  
3 placebo-controlled studies, there was one  
4 anaphylactic reaction in a placebo-controlled  
5 study. In long-term studies, there was one  
6 additional case of anaphylaxis.

7 This case is interesting. The patient had  
8 received four infusions in a prior study, had an  
9 interval of 300 days before receiving his first  
10 infusion in Crohn's Disease Study 251, and had an  
11 anaphylactic reaction. This is interesting to us  
12 because of the theoretical possibility that the  
13 antibody formation might be higher in patients who  
14 are not dosed regularly.

15 I have talked a lot about or some about  
16 anaphylactic reactions. I should mention that skin  
17 and subcutaneous tissue disorder reactions were  
18 actually the most common hypersensitivity infusion  
19 reactions in the multiple sclerosis studies.

20 They occurred in 4.6 percent of the  
21 natalizumab-treated patients compared to 2.2  
22 percent of the placebo-treated patients. Of the

1 reactions categorized under the broad umbrella of  
2 the skin and subcutaneous tissue disorder infusion  
3 reactions, urticaria was the most common, 1.6  
4 percent of patients in the MS studies who were  
5 treated with natalizumab had urticaria compared to  
6 0.3 percent of patients treated with placebo.

7 Per protocol, those patients had to  
8 discontinue from the trial.

9 There were a few delayed hypersensitivity  
10 events. Events reported as serum sickness in  
11 multiple sclerosis studies were actually balanced  
12 in the natalizumab and placebo treated groups.  
13 There was also, in the Crohn's disease studies, a  
14 case reported as a Type 4 hypersensitivity  
15 reaction, and there was one case of leukocytic  
16 classic vasculitis.

17 Most hypersensitivity events occurred  
18 during or immediately after the second infusion,  
19 but some occurred later. One case of anaphylaxis  
20 occurred in association with the 13th infusion.

21 I should mention now, this wasn't observed  
22 in the clinical trial setting, but in case I don't

1 have time to talk about it when I talk about  
2 post-marketing events, there were some events  
3 reported in the serious hypersensitivity events  
4 reported in the post-marketing setting in  
5 association with the first natalizumab infusion.  
6 That was not observed in the clinical trial  
7 setting.

8 [Slide.]

9 The third and final major safety issue I  
10 am going to discuss today is carcinogenicity, and  
11 that is a concern, more a theoretical concern at  
12 this point. Tumor immunosurveillance is mediated  
13 by T-lymphocytes because natalizumab interferes  
14 with their trafficking. We are concerned that it  
15 has the potential to increase the risk of cancer.

16 In the multiple sclerosis  
17 placebo-controlled studies, malignancies were  
18 balanced in natalizumab and placebo-treated  
19 patients. I have listed on this slide the types of  
20 malignancies that were observed just in  
21 natalizumab-treated patients.

22 You can see there were no cases of

1 leukemia or lymphoma, no particularly unusual types  
2 or patterns of malignancies. In Crohn's disease  
3 studies, malignancies were more frequently reported  
4 in the natalizumab group compared to the placebo  
5 group, 0.6 percent versus 0.2 percent, but as you  
6 will remember, the number of infusions the patients  
7 received was small. Biological plausibility I  
8 think is quite low.

9 [Slide.]

10 I have listed again the types of neoplasms  
11 observed in natalizumab-treated patients. In the  
12 Crohn's disease studies, I listed all neoplasms on  
13 this slide rather than just malignancies.

14 I thought it was of note that a meningioma  
15 and a craniopharyngioma were picked up during the  
16 dose suspension safety evaluation study when all  
17 patients were assessed to see if there were any  
18 additional cases of PML.

19 Now, I have saved the most concerning case  
20 potentially, I have listed it last. There was one  
21 case of a lymphoma, and this is the only case of a  
22 leukemia or lymphoma that has been observed in all



1 the clinical trials, and basically, in all patients  
2 treated with natalizumab, there were no leukemias  
3 or lymphomas observed in the post-marketing  
4 setting, the brief post-marketing setting.

5 [Slide.]

6 Just a little bit about this case. It was  
7 a 49-year-old man who had received six infusions of  
8 natalizumab in the course of two Crohn's disease  
9 studies, from September 2004 to February 2005.

10 On his screening examination in September  
11 of 2004, it was noted that he had submandibular  
12 lymphadenopathy. Subsequent examinations, though,  
13 this lymphadenopathy wasn't noted.

14 He had a history of infliximab therapy.  
15 He had received eight doses, and he was taking  
16 6-mercaptopurine at the time that he was taking  
17 natalizumab.

18 In August of 2005, he presented with  
19 enlarging lymph nodes that were painful, and he was  
20 diagnosed with a B-cell lymphoma. He had a CT and  
21 a biopsy that established this diagnosis. The  
22 histological type, though, is not known to us. At

1 this point, clinical details beyond what I have  
2 told you are pending on this case.

3 [Slide.]

4 I think that I have a minute to talk about  
5 serious adverse events that were reported in the  
6 post-marketing setting.

7 Primarily, I want to emphasize the two  
8 cases of herpes central nervous system infections  
9 that were reported. These are concerning to us  
10 particularly because of our concerns about  
11 cell-mediated immune compromise and because  
12 consistently, although the incidence difference was  
13 small, we observed an increase in herpes infections  
14 in the placebo-controlled trials in  
15 natalizumab-treated patients in both the MS and the  
16 Crohn's disease trials.

17 So, there were two herpes central nervous  
18 system infections. One case of herpes, HSV-2  
19 encephalitis, and the patient died. It was a  
20 patient with secondary progressive MS who had a  
21 history of methotrexate therapy lifetime and  
22 Novantrone therapy, actually had received a

1 lifetime maximum dose. Had one infusion of  
2 natalizumab, had viral symptoms.

3 Three months later, presented with  
4 seizures, was diagnosed as HSV-2 encephalitis by  
5 the appropriate CSF studies. Acyclovir was  
6 initiated, but the patient died the next day. The  
7 temporal relationship in this case is not typical  
8 certainly given that there was a three-month  
9 interval.

10 The temporal relationship in the second  
11 case is also a little bit interesting. This was a  
12 patient, a healthier patient, not on any other  
13 immunosuppressive medications, who was diagnosed  
14 with herpes meningitis basically right after  
15 receiving her first natalizumab infusion.

16 She had a history of migraine headaches,  
17 received natalizumab dose I believe in the morning,  
18 later that day had a headache, thought it was her  
19 usual migraine, but it didn't get better with her  
20 usual treatment.

21 Two days later she was admitted, diagnosed  
22 with herpes meningitis, but she recovered and did

1 well with appropriate treatment.

2 In terms of the malignancies that were  
3 reported in the post-marketing setting, again, no  
4 leukemias and lymphomas, which is an important  
5 point. There was a case of ovarian cancer, a case  
6 of endometrial cancer, three cases of skin cancer  
7 including one case of melanoma.

8 Hypersensitivity reactions and infections  
9 were the most commonly reported serious events, but  
10 they don't shed any more light on natalizumab's  
11 risk profile than the clinical trials did, so I am  
12 not going to discuss those cases any further.

13 [Slide.]

14 I would like to summarize briefly the  
15 three key safety issues starting with infections  
16 other than progressive multifocal  
17 leukoencephalopathy.

18 The types of infections that we observed  
19 suggest the possibility of a compromise in  
20 cell-mediated immunity. The herpes infections, the  
21 lower respiratory tract infections that were  
22 observed in both the multiple sclerosis trials,

1 although there weren't atypical pathogens, there  
2 was an increased risk of all lower respiratory  
3 tract infections and serious pneumonias, and, of  
4 course, the atypical lower respiratory tract  
5 infections that were observed in the Crohn's  
6 disease trials are of concern to us, and the cases  
7 of viral meningitis that were observed.

8           The role of concomitant medications and  
9 intercurrent illnesses in the pathogenesis of these  
10 infections is unclear, and, of course, that's the  
11 huge and difficult question before us.

12           I would like to mention on the summary,  
13 this summary slide, that the relative risk for  
14 infections was similar with monotherapy and  
15 combination therapy. In the combination therapy  
16 studies, patients tended to get more infections,  
17 but it was balanced in the natalizumab and placebo  
18 treatment groups.

19           As I mentioned, there was no clear  
20 association between increasing numbers of  
21 natalizumab infusions and the risk for infection.

22           [Slide.]

1 In terms of immunogenicity, antibody  
2 formation to anti-natalizumab occurred in  
3 approximately 10 percent of patients. Persistently  
4 positive antibodies were associated with infusion  
5 reactions, hypersensitivity reactions, increased  
6 multiple sclerosis relapses and Crohn's disease  
7 exacerbations, and a decreased incidence of  
8 infections supporting that natalizumab is  
9 associated with an increased risk for infections.

10 Anaphylactic reactions occurred in 0.4  
11 percent of natalizumab-treated patients with  
12 multiple sclerosis overall and in 5 percent of  
13 antibody-positive patients, a striking difference.

14 Hypersensitivity reactions were most  
15 common with the second infusion, but may occur  
16 much, much later.

17 [Slide.]

18 In terms of carcinogenicity, there was no  
19 evidence of an increase in risk for malignancies in  
20 the multiple sclerosis studies. There was one  
21 lymphoma observed in a patient who participated in  
22 a long-term Crohn's disease trial. It should be

1 noted he was also on 6-mercaptopurine and had a  
2 history of infliximab therapy. Those medications  
3 are associated with an increased incidence of  
4 malignancies themselves.

5           There have been no leukemias observed in  
6 the clinical trial setting or the post-marketing  
7 setting, but this is really the key point in terms  
8 of carcinogenicity, and it's a fairly obvious one,  
9 but I think it is worth making, that longer  
10 exposures will be needed before the risk for  
11 malignancies can be adequately assessed.

12           So, this is something that we are going to  
13 have to keep our eye on in addition obviously, to  
14 infections and hypersensitivity reactions if there  
15 is market reintroduction of natalizumab.

16           [Slide.]

17           I would also like to acknowledge--I will  
18 say Tysabri for the first time in the  
19 presentation--the Tysabri Review Team. Everyone  
20 has contributed to my understanding of the safety  
21 profile, and I would just like to acknowledge  
22 everyone, and apologize to people I have left off

1 the slide.

2 And I would like to introduce our next  
3 speaker, Dr. Diane Wysowski from the FDA's Office  
4 of Drug Safety unless there are, first, points of  
5 clarification for me. I don't know if we have time  
6 for that .

7 DR. KIEBURTZ: Dr. Hughes.

8 DR. A. HUGHES: Yes.

9 DR. M. HUGHES: I have a question about  
10 mortality. As I understand it, there are two  
11 PML-related deaths, but I want to try and put that  
12 in the context of other mortality that was seen in  
13 the overall experience with this drug.

14 What I am not clear about is how many  
15 total deaths are we talking about amongst  
16 drug-exposed subjects, how many are related to  
17 other infections, non-PML, and are any of the  
18 deaths related or thought to be related to MS?

19 DR. A. HUGHES: I would like to answer  
20 this question, if I may, at my seat where I have my  
21 notes.

22 In the development program overall, the



1 clinical trial development program, there are 17  
2 deaths overall. Thirteen of them were on  
3 natalizumab-treated patients, the rest obviously  
4 were in placebo-treated patients. Five of those  
5 were in multiple sclerosis studies, six were in  
6 Crohn's disease studies, and two were in the  
7 rheumatoid arthritis studies.

8 In terms of causes of death, I can briefly  
9 run through them. There was one malignancy, a  
10 melanoma. There were four infections, the two  
11 cases of PML, the case of pulmonary aspergillosis,  
12 the case of pneumocystis pneumonia. There was also  
13 a suicide.

14 There was an acute myocardial infarction  
15 with left ventricular rupture, a case of accidental  
16 carbon dioxide asphyxiation, respiratory distress  
17 secondary to multiple sclerosis progression. This  
18 was in a 5-year-old girl who received natalizumab  
19 in a compassionate use study.

20 There was a case of severe Crohn's disease  
21 exacerbation with multi-organ system failure.  
22 There was a case of respiratory failure due to the

1 procedural complication that occurred after a  
2 central line insertion, and there was the case of  
3 end-stage rheumatic pulmonary disease.

4 That was in the trials. There were five  
5 deaths in the post-marketing setting through the  
6 safety cutoff date, one case of suicide, one case  
7 of ovarian cancer, the case of herpes encephalitis,  
8 a death due to a motor vehicle accident, and a  
9 urinary tract infection in a very sick patient with  
10 multiple sclerosis who had other medical problems,  
11 and that case was actually reported by a family  
12 member, and there aren't too many details about  
13 that.

14 DR. SEJVAR: Just a real quick question.  
15 The cases of viral meningitis, were they  
16 substantiated cases of viral meningitis, or was  
17 there the possibility of aseptic meningitis from  
18 the agent entertained?

19 DR. A. HUGHES: I believe that they were  
20 substantiated cases of viral meningitis although I  
21 will have to look. I will have to get back to you  
22 on that tomorrow.

1 MS. SITCOV: Are the number of deaths in  
2 these studies, 1801 and 1802, separate from the  
3 PML, are those high numbers for studies like this,  
4 or are these conservative numbers? I mean how many  
5 people die from these kinds of studies?

6 DR. A. HUGHES: Dr. Katz and others, and  
7 Dr. Walton may be able to give a better perspective  
8 on this than I can. I think it's fairly typical,  
9 but--do you have anything to add?

10 DR. WALTON: We were not impressed that  
11 the overall mortality rate was markedly different  
12 than we might expect in MS studies. Of course,  
13 different studies use different populations, so it  
14 is not possible to really compare the precise  
15 mortality rates, so we tend to focus more on the  
16 nature of the mortality, but the absolute rates did  
17 not strike us as notably different.

18 MS. SITCOV: So, you don't look at this  
19 and say it's striking.

20 DR. WALTON: No.

21 DR. A. HUGHES: I think that the fact that  
22 the deaths were not notably increased in

1   natalizumab-treated patients compared to  
2   placebo-treated patients is informative, and not  
3   for that question.

4                   Risk Minimization Action Plan

5           DR. WYSOWSKI: Good morning. My name is  
6   Diane Wysowski and I am an epidemiologist in the  
7   Division of Drug Risk Evaluation, Office of Drug  
8   Safety, FDA.

9           I am here to review and discuss the  
10   Tysabri Risk Minimization Action Plan submitted by  
11   the company sponsors Biogen Idec and Elan. The  
12   information presented is based on our understanding  
13   of several versions of the plan and on discussions  
14   between the sponsors and the FDA.

15           Some of the changes in the plan came in  
16   yesterday, and I will mention the changes that have  
17   been made although my slides have not been updated.

18           [Slide.]

19           In this presentation, I will review the  
20   main features of the plan including its goals, its  
21   methods, the Tysabri Registry that is primarily for  
22   PML surveillance and opportunistic infection

## **EXHIBIT 16**

Final

## **TYSABRI® (natalizumab)**

### **WARNING**

TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Although the cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with TYSABRI® monotherapy.

- Because of the risk of PML, TYSABRI® is available only through a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI® must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program (see **WARNINGS, Progressive Multifocal Leukoencephalopathy; and WARNINGS, Prescribing, Distribution, and Administration Program for TYSABRI®**).
- Healthcare professionals should monitor patients on TYSABRI® for any new sign or symptom that may be suggestive of PML. TYSABRI® dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended (see **CONTRAINDICATIONS and WARNINGS, Progressive Multifocal Leukoencephalopathy**).

### **DESCRIPTION**

TYSABRI® (natalizumab) is a recombinant humanized IgG4κ monoclonal antibody produced in murine myeloma cells. Natalizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to α4-integrin. The molecular weight of natalizumab is 149 kilodaltons. TYSABRI® is supplied as a sterile, colorless, and clear to slightly opalescent concentrate for intravenous (IV) infusion.

Each 15 mL dose contains 300 mg natalizumab; 123 mg sodium chloride, USP; 17.0 mg sodium phosphate, monobasic, monohydrate, USP; 7.24 mg sodium phosphate, dibasic, heptahydrate, USP; 3.0 mg polysorbate 80, USP/NF, in water for injection, USP at pH 6.1.

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## CLINICAL PHARMACOLOGY

### General

TYSABRI® binds to the  $\alpha 4$ -subunit of  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$  integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the  $\alpha 4$ -mediated adhesion of leukocytes to their counter-receptor(s). The receptors for the  $\alpha 4$  family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium, and mucosal addressin cell adhesion molecule-1 (MadCAM-1) present on vascular endothelial cells of the gastrointestinal tract. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. *In vitro*, anti- $\alpha 4$ -integrin antibodies also block  $\alpha 4$ -mediated cell binding to ligands such as osteopontin and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). *In vivo*, TYSABRI® may further act to inhibit the interaction of  $\alpha 4$ -expressing leukocytes with their ligand(s) in the extracellular matrix and on parenchymal cells, thereby inhibiting further recruitment and inflammatory activity of activated immune cells.

The specific mechanism(s) by which TYSABRI® exerts its effects in multiple sclerosis have not been fully defined. In multiple sclerosis, lesions are believed to occur when activated inflammatory cells, including T-lymphocytes, cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and their counter-receptors present on endothelial cells of the vessel wall. The clinical effect of natalizumab in multiple sclerosis may be secondary to blockade of the molecular interaction of  $\alpha 4\beta 1$ -integrin expressed by inflammatory cells with VCAM-1 on vascular endothelial cells, and with CS-1 and/or osteopontin expressed by parenchymal cells in the brain. Data from an experimental autoimmune encephalitis animal model of multiple sclerosis demonstrate reduction of leukocyte migration into brain parenchyma and reduction of plaque formation detected by magnetic resonance imaging (MRI) following repeated administration of natalizumab. The clinical significance of these animal data is unknown.

### Pharmacokinetics

Following the repeat intravenous administration of a 300 mg dose of natalizumab to patients with multiple sclerosis, the mean maximum observed serum concentration was  $110 \pm 52$  mcg/mL. Mean average steady-state trough concentrations ranged from 23 mcg/mL to 29 mcg/mL. The observed time to steady-state was approximately 24 weeks after every 4 weeks of dosing. The mean half-life, volume of distribution, and clearance of natalizumab were  $11 \pm 4$  days,  $5.7 \pm 1.9$  L, and  $16 \pm 5$  mL/hour, respectively.

The effects of covariates such as body weight, age, gender, and presence of anti-natalizumab antibodies on natalizumab pharmacokinetics were investigated in a population pharmacokinetic study. Natalizumab clearance increased with body weight in a less than proportional manner such that a 43% increase in body weight resulted in a 32% increase in clearance. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 3-fold (see **ADVERSE REACTIONS, Immunogenicity**). Age (18 to 62 years) and gender did not influence natalizumab pharmacokinetics.

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Pharmacokinetics of TYSABRI® in pediatric patients with multiple sclerosis or patients with renal or hepatic insufficiency have not been studied.

### **Pharmacodynamics**

TYSABRI® administration increases the number of circulating leukocytes (including lymphocytes, monocytes, basophils, and eosinophils) due to inhibition of transmigration out of the vascular space. TYSABRI® does not affect the number of circulating neutrophils (**see PRECAUTIONS, Laboratory Tests**).

### **CLINICAL STUDIES**

TYSABRI® was evaluated in two randomized, double-blind, placebo-controlled trials in patients with multiple sclerosis. Both studies enrolled patients who experienced at least one clinical relapse during the prior year and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.0.

In both studies, neurological evaluations were performed every 12 weeks and at times of suspected relapse. Magnetic resonance imaging evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study 1 enrolled patients who had not received any interferon-beta or glatiramer acetate for at least the previous 6 months; approximately 94% had never been treated with these agents. Median age was 37, with a median disease duration of 5 years. Patients were randomized in a 2:1 ratio to receive TYSABRI® 300 mg IV infusion (n=627) or placebo (n=315) every 4 weeks for up to 28 months (30 infusions).

Study 2 enrolled patients who had experienced one or more relapses while on treatment with AVONEX® (Interferon beta-1a) 30 mcg intramuscularly (IM) once weekly during the year prior to study entry. Median age was 39, with a median disease duration of 7 years. Patients were evenly randomized to receive TYSABRI® 300 mg (n=589) or placebo (n=582) every 4 weeks for up to 28 months (30 infusions). All patients continued to receive AVONEX® 30 mcg IM once weekly.

The efficacy of TYSABRI® alone was not compared with the efficacy of TYSABRI® plus AVONEX®.

Results for each study are shown in Tables 1 and 2. Median time on study drug was 120 weeks in each study. Safety and efficacy of treatment with TYSABRI® beyond two years are not known.

The primary endpoint at 2 years was time to onset of sustained increase in disability, defined as an increase of at least 1 point on the EDSS from baseline EDSS  $\geq 1.0$  that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS=0 that was sustained for 12 weeks. Time to onset of sustained increase in disability was longer in TYSABRI®-treated patients than in placebo-treated patients in Studies 1 (Figure 1) and 2. The proportion of patients



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with increased disability and the annualized relapse rate were also lower in TYSABRI®-treated patients than in placebo-treated patients in Studies 1 and 2 (Tables 1 and 2).

Changes in MRI findings often do not correlate with changes in the clinical status of patients (e.g., disability progression). The prognostic significance of the MRI findings in these studies has not been evaluated.

**Table 1. Clinical and MRI Endpoints in Study 1 (Monotherapy Study) at 2 Years**

	<b>TYSABRI®</b> n=627	<b>Placebo</b> n=315
<b>Clinical Endpoints</b>		
Percentage with sustained increase in disability	17%	29%
Relative Risk Reduction	42% (95% CI 23%, 57%)	
Annualized relapse rate	0.22	0.67
Relative reduction (percentage)	67%	
Percentage of patients remaining relapse-free	67%	41%
<b>MRI Endpoints</b>		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	5.0
Percentage of patients with*:		
0 lesions	57%	15%
1 lesion	17%	10%
2 lesions	8%	8%
3 or more lesions	18%	68%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with:		
0 lesions	97%	72%
1 lesion	2%	12%
2 or more lesions	1%	16%

All analyses were intent-to-treat. For each endpoint, p<0.001. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS and age; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

Annualized relapse rate is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

\*Values do not total 100% due to rounding.

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**Table 2. Clinical and MRI Endpoints in Study 2 (Add-On Study) at 2 Years**

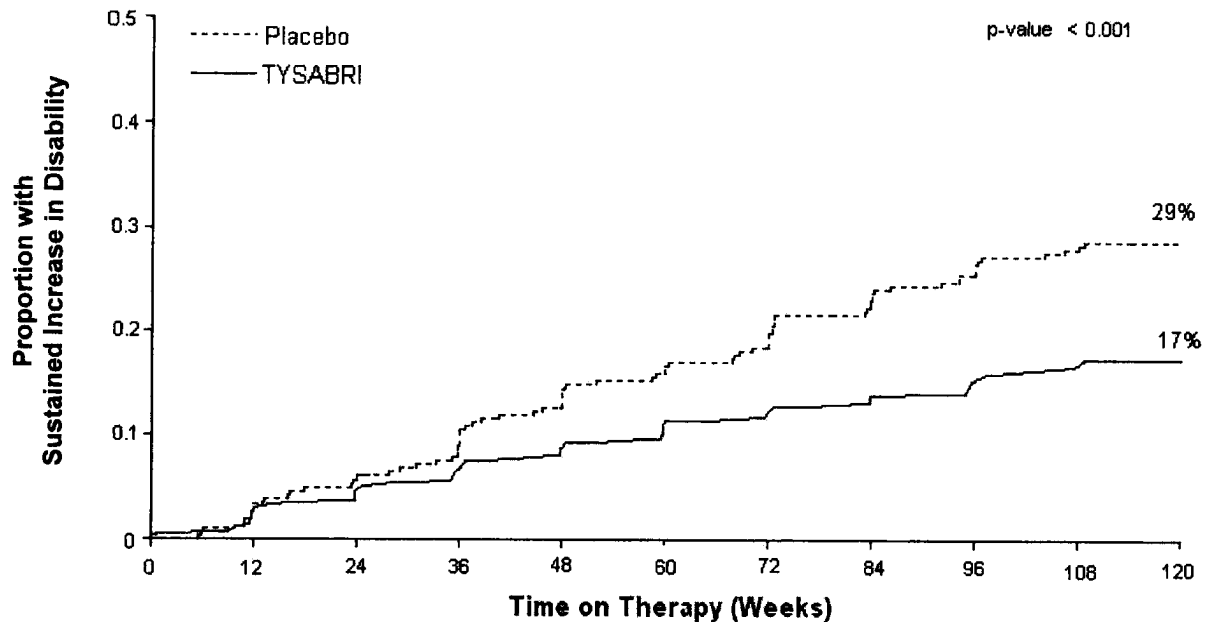
	<b>TYSABRI® plus AVONEX® n=589</b>	<b>Placebo plus AVONEX® n=582</b>
<b>Clinical Endpoints</b>		
Percentage with sustained increase in disability	23%	29%
Relative Risk Reduction	24% (95% CI 4%, 39%)	
Annualized relapse rate	0.33	0.75
Relative reduction (percentage)	56%	
Percentage of patients remaining relapse-free	54%	32%
<b>MRI Endpoints</b>		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	3.0
Percentage of patients with*:		
0 lesions	67%	30%
1 lesion	13%	9%
2 lesions	7%	10%
3 or more lesions	14%	50%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with*:		
0 lesions	96%	75%
1 lesion	2%	12%
2 or more lesions	1%	14%

All analyses were intent-to-treat. For disability accumulation  $p=0.024$ , for all other endpoints,  $p<0.001$ . Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

Annualized relapse rate is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

\*Values do not total 100% due to rounding.

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**Figure 1. Time to Increase in Disability Sustained for 12 Weeks in Study 1****INDICATIONS AND USAGE**

TYSABRI® is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. The safety and efficacy of TYSABRI® beyond two years are unknown.

Because TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (**see BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy**), TYSABRI® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies.

Safety and efficacy in patients with chronic progressive multiple sclerosis have not been studied.

**CONTRAINDICATIONS**

TYSABRI® should not be administered to patients with known hypersensitivity to TYSABRI® or any of its components.

TYSABRI® is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) (**see BOXED WARNING and WARNINGS**).

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## **WARNINGS**

### **Progressive Multifocal Leukoencephalopathy (PML)**

**Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus that typically occurs in patients that are immunocompromised, has occurred in 3 patients who received TYSABRI® in clinical trials (see BOXED WARNING). Two cases of PML were observed in 1869 patients with multiple sclerosis treated for a median of 120 weeks. The third case occurred among 1043 patients with Crohn's disease after the patient received 8 doses. The absolute risk for PML in patients treated with TYSABRI® cannot be precisely estimated, and factors that might increase an individual patient's risk for PML have not been identified. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI® will mitigate the disease. There is limited experience beyond 2 years of treatment. The relationship between the risk of PML and the duration of treatment is unknown.**

**All three cases of PML occurred in patients who were concomitantly exposed to immunomodulators (interferon beta in the patients with multiple sclerosis) or were immunocompromised due to recent treatment with immunosuppressants (e.g., azathioprine in the patient with Crohn's disease). Ordinarily, therefore, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not be treated with TYSABRI®. However, the number of cases is too few and the number of patients treated too small to reliably conclude that the risk of PML is lower in patients treated with TYSABRI® alone than in patients who are receiving other drugs that decrease immune function or who are otherwise immunocompromised.**

**Because of the risk of PML, TYSABRI® is available only under a special restricted distribution program, the TOUCH™ Prescribing Program.**

**An MRI scan should be obtained prior to initiating therapy with TYSABRI®. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML. Healthcare professionals should monitor patients on TYSABRI® for any new sign or symptom suggestive of PML. TYSABRI® dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.**

### **Prescribing, Distribution, and Administration Program for TYSABRI®**

**TYSABRI® is available only under a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI® must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing**

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Program (see **BOXED WARNING** and/or contact the TOUCH™ Prescribing Program at 1-800-456-2255).

To enroll in the TOUCH™ Prescribing Program, prescribers and patients are required to understand the risks of treatment with TYSABRI®, including PML and other opportunistic infections. Prescribers are required to understand the information in the Prescribing Information and to be able to:

- Diagnose and manage opportunistic infections and PML, or be prepared to refer patients to specialists with these abilities.
- Educate patients on the benefits and risks of treatment with TYSABRI®, provide them with the Medication Guide, instruct them to read it, and encourage them to ask questions when considering TYSABRI®. Patients may be educated by the enrolled prescriber or a healthcare provider under that prescriber's direction.
- Review the TOUCH™ Prescriber/Patient Enrollment form for TYSABRI® with the patient and answer all questions.
- As part of the initial prescription process for TYSABRI®, obtain the patient's signature and initials on the TOUCH™ program enrollment form, sign it, place the original signed form in the patient's medical record, send a copy to Biogen Idec, and give a copy to the patient.
- Report serious opportunistic and atypical infections with TYSABRI® to Biogen Idec at 1-800-456-2255 and to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088.
- Evaluate the patient 3 months after the first infusion, 6 months after the first infusion, and every 6 months thereafter.
- Determine every 6 months whether patients should continue on treatment and if so reauthorize treatment every 6 months.
- Submit to Biogen Idec the TYSABRI® Patient Status Report and Reauthorization Questionnaire 6 months after initiating treatment and every 6 months thereafter.

### Information for Patients

Patients should be fully counseled on and understand the risks and benefits of TYSABRI® before an initial prescription is written. The patient may be educated by either the enrolled prescriber or a healthcare provider under that prescriber's direction.

### PATIENTS WHO ARE PRESCRIBED TYSABRI® SHOULD BE INSTRUCTED TO:

- Read the Medication Guide before starting TYSABRI® and before each TYSABRI® infusion.
- Promptly report any continuously worsening symptoms that persist over several days to their prescriber (see **BOXED WARNING** and **WARNINGS, Progressive Multifocal Leukoencephalopathy**).
- Inform all of their physicians that they are receiving TYSABRI®.
- Plan to see their prescriber 3 months after the first infusion, 6 months after the first infusion, and at least as frequently as every 6 months thereafter.

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If patients experience symptoms consistent with a hypersensitivity reaction (e.g., urticaria with or without associated symptoms) during or following an infusion of TYSABRI<sup>®</sup>, they should report these symptoms to their prescriber immediately (see **WARNINGS, Hypersensitivity**).

### **Hypersensitivity**

TYSABRI<sup>®</sup> has been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. These reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Generally, these reactions are associated with antibodies to TYSABRI<sup>®</sup>.

If a hypersensitivity reaction occurs, discontinue administration of TYSABRI<sup>®</sup> and initiate appropriate therapy (see **ADVERSE REACTIONS, Infusion-related Reactions**). Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI<sup>®</sup>. The possibility of antibodies to TYSABRI<sup>®</sup> should be considered in patients who have hypersensitivity reactions (see **ADVERSE REACTIONS, Immunogenicity**).

### **Immunosuppression**

The immune system effects of TYSABRI<sup>®</sup> may increase the risk for infections. In Study 1, certain types of infections, including pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections, occurred more often in TYSABRI<sup>®</sup>-treated patients than in placebo-treated patients (see **WARNINGS, Progressive Multifocal Leukoencephalopathy (PML); and ADVERSE REACTIONS, General and Infections**). One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI<sup>®</sup> in Study 1.

Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of TYSABRI<sup>®</sup> alone (see **BOXED WARNING; WARNINGS, Progressive Multifocal Leukoencephalopathy; and ADVERSE REACTIONS, Infections**). The safety and efficacy of TYSABRI<sup>®</sup> in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established.

Concurrent use of short courses of corticosteroids was associated with an increase in infections in Studies 1 and 2. However, the increase in infections in TYSABRI<sup>®</sup>-treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids.

## **PRECAUTIONS**

### **Information for Patients**

See **WARNINGS, Information for Patients**

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### **Laboratory Tests**

TYSABRI® induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persist during TYSABRI® exposure, but are reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils are not observed. TYSABRI® induces mild decreases in hemoglobin levels that are frequently transient.

### **Drug Interactions**

See **BOXED WARNING** and **WARNINGS, Immunosuppression**.

### **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

No clastogenic or mutagenic effects of natalizumab were observed in the Ames test or *in vitro* chromosomal aberration assay in human lymphocytes. Natalizumab showed no effects in *in vitro* assays of  $\alpha$ 4-integrin positive human tumor line proliferation/cytotoxicity. Xenograft transplantation models in SCID and nude mice with two  $\alpha$ 4-integrin positive human tumor lines (leukemia, melanoma) demonstrated no increase in tumor growth rates or metastasis resulting from natalizumab treatment.

Reductions in female guinea pig fertility were observed in one study at dose levels of 30 mg/kg, but not at the 10 mg/kg dose level (2.3-fold the clinical dose). A 47% reduction in pregnancy rate was observed in guinea pigs receiving 30 mg/kg relative to control. Implantations were seen in only 36% of animals having corpora lutea in the 30 mg/kg group versus 66-72% in the other groups. Natalizumab did not affect male fertility at doses up to 7-fold the clinical dose.

### **Pregnancy (Category C)**

There are no adequate and well-controlled studies of TYSABRI® therapy in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking TYSABRI®, discontinuation of TYSABRI® should be considered.

If a woman becomes pregnant while taking TYSABRI®, consider enrolling her in the TYSABRI® Pregnancy Exposure Registry by calling 1-800-456-2255.

In reproductive studies in monkeys and guinea pigs, there was no evidence of teratogenic effects at doses up to 30 mg/kg (7 times the human clinical dose based on a body weight comparison). In one study where female guinea pigs were exposed to natalizumab during the second half of pregnancy, a small reduction in pup survival was noted at post-natal day 14 with respect to control (3 pups/litter for the group treated with 30 mg/kg natalizumab and 4.3 pups/litter for the control group). In one of five studies that exposed monkeys or guinea pigs during pregnancy, the number of abortions in treated (30 mg/kg) monkeys was 33% versus 17% in controls. No effects on abortion rates were noted in any other study. TYSABRI® underwent trans-placental transfer and produced *in utero* exposure in developing guinea pigs and cynomolgus monkeys. When



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pregnant dams were exposed to natalizumab at approximately 7-fold the clinical dose, serum levels in fetal animals at delivery were approximately 35% of maternal serum natalizumab levels. A study in pregnant cynomolgus monkeys treated at 2.3-fold the clinical dose demonstrated natalizumab-related changes in the fetus. These changes included mild anemia, reduced platelet count, increased spleen weights, and reduced liver and thymus weights associated with increased splenic extramedullary hematopoiesis, thymic atrophy, and decreased hepatic hematopoiesis. In offspring born to mothers treated with natalizumab at 7-fold the clinical dose, platelet counts were also reduced. This effect was reversed upon clearance of natalizumab. There was no evidence of anemia in these offspring. Offspring exposed *in utero* and via breast milk had no natalizumab-related changes in the lymphoid organs and had normal immune response to challenge with a T-cell dependent antigen.

## Nursing Mothers

It is not known whether TYSABRI® is excreted in human milk. Because many drugs and immunoglobulins are excreted in human milk, and because the potential for serious adverse reactions is unknown, discontinuation of TYSABRI® or alternatives to nursing should be considered.

## Geriatric Use

Clinical studies of TYSABRI® did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients.

## Pediatric Use

Safety and effectiveness of TYSABRI® in pediatric patients with multiple sclerosis below the age of 18 have not been studied. TYSABRI® is not indicated for use in pediatric patients.

## Immunizations

No data are available on the effects of vaccination in patients receiving TYSABRI®. No data are available on the secondary transmission of infection by live vaccines in patients receiving TYSABRI®.

## ADVERSE REACTIONS

### General

The most frequently reported serious adverse events in Study 1 (see **CLINICAL STUDIES**) with TYSABRI® were infections (3.2% versus 2.6% in placebo, including urinary tract infection [0.8% versus 0.3%] and pneumonia [0.6% versus 0%]), acute hypersensitivity reactions (1.1% versus 0.3%, including anaphylaxis/anaphylactoid reaction [0.8% versus 0%]), depression (1.0% versus 1.0%, including suicidal ideation or attempt [0.6% versus 0.3%]), and cholelithiasis (1.0% versus 0.3%). In Study 2, serious adverse events of appendicitis were also more common in



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patients who received TYSABRI® (0.8% versus 0.2% in placebo) (see **WARNINGS, Hypersensitivity and ADVERSE REACTIONS, Infections**).

The most frequently reported adverse reactions resulting in clinical intervention (i.e., discontinuation of TYSABRI®), were urticaria (1%) and other hypersensitivity reactions (1%) (see **WARNINGS, Hypersensitivity**).

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of TYSABRI® cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

A total of 1617 multiple sclerosis patients in controlled studies received TYSABRI®, with a median duration of exposure of 28 months.

Table 3 enumerates adverse events and selected laboratory abnormalities that occurred in Study 1 at an incidence of at least 1 percentage point higher in TYSABRI®-treated patients than was observed in placebo-treated patients.

**Table 3. Adverse Reactions in Study 1 (Monotherapy Study)**

<b>Adverse Events (Preferred Term)</b>	<b>TYSABRI® n=627 Percentage</b>	<b>Placebo n=312 Percentage</b>
<b>General</b>		
Headache	38%	33%
Fatigue	27%	21%
Arthralgia	19%	14%
Chest discomfort	5%	3%
Acute hypersensitivity reactions**	4%	<1%
Other hypersensitivity reactions**	5%	2%
Seasonal allergy	3%	2%
Rigors	3%	<1%
Weight increased	2%	<1%
Weight decreased	2%	<1%
<b>Infection</b>		
Urinary tract infection	21%	17%
Lower respiratory tract infection	17%	16%
Gastroenteritis	11%	9%
Vaginitis*	10%	6%
Tooth infections	9%	7%
Herpes	8%	7%
Tonsillitis	7%	5%

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<b>Adverse Events (Preferred Term)</b>	<b>TYSABRI® n=627 Percentage</b>	<b>Placebo n=312 Percentage</b>
<b>Psychiatric</b>		
Depression	19%	16%
<b>Musculoskeletal/Connective Tissue Disorders</b>		
Pain in extremity	16%	14%
Muscle cramp	5%	3%
Joint swelling	2%	1%
<b>Gastrointestinal</b>		
Abdominal discomfort	11%	10%
Diarrhea NOS	10%	9%
Abnormal liver function test	5%	4%
<b>Skin</b>		
Rash	12%	9%
Dermatitis	7%	4%
Pruritus	4%	2%
Night sweats	1%	0%
<b>Menstrual Disorders*</b>		
Irregular menstruation	5%	4%
Dysmenorrhea	3%	<1%
Amenorrhea	2%	1%
Ovarian cyst	2%	<1%
<b>Neurologic Disorders</b>		
Somnolence	2%	<1%
Vertigo	6%	5%
<b>Renal and Urinary Disorders</b>		
Urinary incontinence	4%	3%
Urinary urgency/frequency	9%	7%
<b>Injury</b>		
Limb injury NOS	3%	2%
Skin laceration	2%	<1%
Thermal burn	1%	<1%

\*Percentage based on female patients only.

\*\* Acute versus other hypersensitivity reactions are defined as occurring within 2 hours post-infusion versus more than 2 hours.

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In Study 2, peripheral edema was more common in patients who received TYSABRI® (5% versus 1% in placebo).

### **Infections**

Progressive Multifocal Leukoencephalopathy (PML) has occurred in 3 patients who received TYSABRI® in clinical trials (see **BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy**). Two cases of PML were observed in the 1869 patients with multiple sclerosis who were treated for a median of 120 weeks. These 2 patients had received TYSABRI in addition to interferon beta-1a (see **BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy**). The third case occurred after 8 doses in one of the 1043 patients with Crohn's disease who were evaluated for PML.

In Studies 1 and 2, the rate of any type of infection was approximately 1.5 per patient-year in both TYSABRI®-treated patients and placebo-treated patients. The infections were predominately upper respiratory tract infections, influenza, and urinary tract infections.

In Study 1, the incidence of serious infection was approximately 3% in TYSABRI®-treated patients and placebo-treated patients. Most patients did not interrupt treatment with TYSABRI® during infections.

The only opportunistic infection in the multiple sclerosis clinical trials was a case of cryptosporidial gastroenteritis with a prolonged course.

In clinical studies for indications other than multiple sclerosis, opportunistic infections (e.g., pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been uncommonly observed in TYSABRI®-treated patients; some of these patients were receiving concurrent immunosuppressants (see **WARNINGS, Immunosuppression**). Two serious non-bacterial meningitides occurred in TYSABRI®-treated patients compared to none in placebo-treated patients.

In post-marketing experience, one patient who received TYSABRI® developed herpes encephalitis and died; a second patient developed herpes meningitis and recovered with appropriate treatment.

### **Infusion-related Reactions (see WARNINGS, Hypersensitivity)**

An infusion-related reaction was defined in clinical trials as any adverse event occurring within 2 hours of the start of an infusion. Approximately 24% of TYSABRI®-treated multiple sclerosis patients experienced an infusion-related reaction, compared to 18% of placebo-treated patients. Events more common in the TYSABRI®-treated patients included headache, dizziness, fatigue, urticaria, pruritus, and rigors. Acute urticaria was observed in approximately 2% of patients. Other hypersensitivity reactions were observed in 1% of patients receiving TYSABRI®. Serious

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systemic hypersensitivity infusion reactions occurred in <1% of patients. All patients recovered with treatment and/or discontinuation of the infusion.

Patients who became persistently positive for antibodies to TYSABRI® were more likely to have an infusion-related reaction than those who were antibody-negative (see **ADVERSE REACTIONS, Immunogenicity**).

### **Immunogenicity**

Patients in Study 1 were tested for antibodies to natalizumab every 12 weeks. The assays used were unable to detect low to moderate levels of antibodies to natalizumab. Approximately 9% of patients receiving TYSABRI® developed detectable antibodies at least once during treatment. Approximately 6% of patients had positive antibodies on more than one occasion. Approximately 82% of patients who became persistently antibody-positive developed detectable antibodies by 12 weeks. Anti-natalizumab antibodies were neutralizing *in vitro*.

The presence of anti-natalizumab antibodies was correlated with a reduction in serum natalizumab levels. In Study 1, the Week 12 pre-infusion mean natalizumab serum concentration in antibody-negative patients was 14.9 mcg/mL compared to 1.3 mcg/mL in antibody-positive patients. Persistent antibody-positivity was associated with a substantial decrease in the effectiveness of TYSABRI®. The risk of increased disability and the annualized relapse rate were similar in persistently antibody-positive TYSABRI®-treated patients and patients who received placebo. A similar phenomenon was also observed in Study 2.

Infusion-related reactions most often associated with persistent antibody-positivity included urticaria, rigors, nausea, vomiting, headache, flushing, dizziness, pruritus, tremor, feeling cold, and pyrexia. Additional adverse events more common in persistently antibody-positive patients included myalgia, hypertension, dyspnea, anxiety, and tachycardia.

If the presence of persistent antibodies is suspected, antibody testing should be performed. Antibodies may be detected and confirmed with sequential serum antibody tests. Antibodies detected early in the treatment course (e.g., within the first 6 months) may be transient and disappear with continued dosing. Repeat testing at 3 months after the initial positive result is recommended in patients in whom antibodies are detected to confirm that antibodies are persistent. Prescribers should consider the overall benefits and risks of TYSABRI® in a patient with persistent antibodies.

The long-term immunogenicity of TYSABRI® and the effects of low to moderate levels of antibody to natalizumab are unknown. Experience with other monoclonal antibodies suggests that patients who receive therapeutic antibodies after an extended period without treatment may be at higher risk of hypersensitivity reactions than patients who received regularly scheduled treatment. It is not known if this will occur with TYSABRI® (see **WARNINGS, Hypersensitivity and ADVERSE REACTIONS, Infusion-related Reactions**).

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody-positivity in an assay may be influenced by

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several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to TYSABRI® with the incidence of antibodies to other products may be misleading.

## **OVERDOSAGE**

Safety of doses higher than 300 mg has not been adequately evaluated. The maximum amount of TYSABRI® that can be safely administered has not been determined.

## **DOSAGE AND ADMINISTRATION**

Only prescribers registered in the TOUCH™ Prescribing Program may prescribe TYSABRI® (see **BOXED WARNING**).

The recommended dose of TYSABRI® is 300 mg IV infusion every four weeks. Dilute TYSABRI® concentrate 300 mg/15 mL in 100 mL 0.9% Sodium Chloride Injection, USP, and infuse over approximately one hour. Do not administer TYSABRI® as an IV push or bolus injection (see **Preparation Instructions**).

Observe patients during the infusion and for 1 hour after the infusion is complete. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction (see **WARNINGS, Hypersensitivity**).

### **Preparation Instructions**

Use aseptic technique when preparing TYSABRI® solution for IV infusion. Each vial is intended for single use only.

TYSABRI® is a colorless, clear to slightly opalescent concentrate. Inspect the TYSABRI® vial for particulate material prior to dilution and administration. If visible particulates are observed and/or the liquid in the vial is discolored, the vial must not be used. Do not use TYSABRI® beyond the expiration date stamped on the carton or vial.

To prepare the solution, withdraw 15 mL of TYSABRI® concentrate from the vial using a sterile needle and syringe. Inject the concentrate into 100 mL 0.9% Sodium Chloride Injection, USP. No other IV diluents may be used to prepare the TYSABRI® solution.

Gently invert the TYSABRI® solution to mix completely. Do not shake. Inspect the solution visually for particulate material prior to administration.

Following dilution, infuse TYSABRI® solution immediately, or refrigerate solution at 2-8°C, and use within 8 hours. If stored at 2-8°C, allow the solution to warm to room temperature prior to infusion. **DO NOT FREEZE.**

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### **Administration Instructions**

Infuse TYSABRI® 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP over approximately one hour. After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.

Use of filtration devices during administration has not been evaluated. Other medications should not be injected into infusion set side ports or mixed with TYSABRI®.

### **HOW SUPPLIED**

TYSABRI® concentrate is supplied as 300 mg natalizumab in a sterile, single-use vial free of preservatives. Each package contains a single-use vial. NDC 59075-730-15

TYSABRI® is available only through registered infusion centers participating in the TOUCH™ Prescribing Program. To locate these infusion centers, contact Biogen Idec at 1-800-456-2255.

### **Storage**

TYSABRI® single-use vials must be refrigerated between 2-8°C (36°-46°F). Do not use beyond the expiration date stamped on the carton and vial label. DO NOT SHAKE OR FREEZE. Protect from light.

If not used immediately, store the TYSABRI® solution for infusion at 2-8°C (36°-46°F). TYSABRI® solution for infusion must be administered within 8 hours of preparation.

I61061-2 Issue date 06/2006

TYSABRI® (natalizumab)

Manufactured by:  
Biogen Idec Inc.  
14 Cambridge Center  
Cambridge, MA 02142 USA  
1-800-456-2255

Distributed by:  
Elan Pharmaceuticals, Inc.  
San Diego, CA 92121

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TYSABRI® is a registered trademark of Elan Pharmaceuticals, Inc.  
AVONEX® is a registered trademark of Biogen Idec  
TOUCH™ is a trademark of Elan Pharmaceuticals, Inc.

U.S. Patent Numbers: 5,840,299, 6,033,665, 6,602,503, 5,168,062, 5,385,839, 5,730,978

## **EXHIBIT 17**

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <b>RASTETTER WILLIAM H</b>  (Last) (First) (Middle) <b>14 CAMBRIDGE CENTER</b>  (Street) <b>CAMBRIDGE MA 02142</b>  (City) (State) (Zip)	<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIOGEN IDEC INC [ BIIB ]</b>	<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) Executive Chairman
	<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 05/14/2004	
		<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	05/14/2004		J		281,611	D	\$0	371,262 <sup>(1)</sup>	I	by Trust <sup>(2)</sup>
Common Stock								50,367	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					

**Explanation of Responses:**

- Since the date of the reporting person's last ownership report, he transferred 277,611 shares of BIIB common stock to his ex-wife pursuant to a domestic relations order.
- Shares were transferred to a trust of which the reporting person is the trustee. The reporting person disclaims beneficial ownership of the securities except to the extent of his pecuniary interest therein.

**Remarks:**

By: Benjamin S. Harshbarger 05/18/2004  
 For: William H. Rastetter

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.



SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <u>RASTETTER WILLIAM H</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 05/19/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) Executive Chairman  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	05/19/2004		M		25,000	A	\$3.3542	133,162	D	
Common Stock	05/19/2004		S		25,000	D	\$60.03	108,162	D	
Common Stock								371,262	I	by Trust (1)
Common Stock								50,367	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$3.3542	05/19/2004		M			25,000	(3)	01/24/2006	Common Stock	25,000	(2)	108,162	D	

**Explanation of Responses:**

- Shares are held in a trust of which the reporting person is the trustee. The reporting person disclaims beneficial ownership of the securities except to the extent of his pecuniary interest therein.
- Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
- Option becomes exercisable as to 25% of the optioned shares on 1/01/97 and as to the balance of the shares in 36 equal monthly installments thereafter.

**Remarks:**

By: Benjamin S. Harshbarger 05/19/2004  
 For: William H. Rastetter  
 \*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person <b>RASTETTER WILLIAM H</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) Executive Chairman	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 05/24/2004		6. Individual or Joint/Group Filing (Check Applicable Line)  <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	(City)	(State)	(Zip)			

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	05/24/2004		M		29,081	A	\$3.3542	108,162	D	
Common Stock	05/24/2004		S		29,081	D	\$62.5052	79,081	D	
Common Stock								371,262	I	by Trust (1)
Common Stock								50,367	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$3.3542	05/24/2004		M		29,081	(3)	01/24/2006	Common Stock	29,081	(2)	79,081	D	

**Explanation of Responses:**

- Shares are held in a trust of which the reporting person is the trustee. The reporting person disclaims beneficial ownership of the securities except to the extent of his pecuniary interest therein.
- Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
- Option becomes exercisable as to 25% of the optioned shares on 1/01/97 and as to the balance of the shares in 36 equal monthly installments thereafter.

**Remarks:**

By: Benjamin S. Harshbarger  
For: William H. Rastetter  
\*\* Signature of Reporting Person Date

05/26/2004

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**
☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <b>RASTETTER WILLIAM H</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>			5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner  X Officer (give title below) Other (specify below) Executive Chairman		
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 02/15/2005			6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person		
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)					
(Street)	MA	02142						
(City)	(State)	(Zip)						

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	02/15/2005		M		120,313	A	\$3.3542	120,313	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		2,500	D	\$67.51	117,813	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		27,500	D	\$67.56	90,313	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		22,500	D	\$67.6243	67,813	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		7,500	D	\$67.69	60,313	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		5,000	D	\$67.79	55,313	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		10,000	D	\$67.86	45,313	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		32,500	D	\$67.87	12,313	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		7,500	D	\$67.8724	5,313	D	
Common Stock	02/15/2005		S <sup>(1)</sup>		5,313	D	\$67.91	0	D	
Common Stock								371,629 <sup>(2)</sup>	I	by Trust
Common Stock								50,676.77 <sup>(3)</sup>	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned**  
(e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) <sup>(4)</sup>	\$3.3542	02/15/2005		M			120,313	<sup>(5)</sup>	01/24/2006	Common Stock	120,313	<sup>(4)</sup>	0	D	

**Explanation of Responses:**

- Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
- Increase in the amount of indirectly held shares is the result of a transfer of directly held shares into a trust.
- Decrease in the amount of directly held shares is the result of a transfer of directly held shares into a trust.
- Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
- Option became exercisable as to 25% of the optioned shares on 1/25/96 and as to the balance of the shares in 36 equal monthly installments thereafter.

**Remarks:**
 By: Benjamin S. Harshbarger;  
 For: William H. Rastetter  
 \*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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## **EXHIBIT 18**

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 05/24/2004		
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b>  <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	05/24/2004		M		1,500	A	\$7.31	35,075	D	
Common Stock	05/24/2004		S <sup>(1)</sup>		1,500	D	\$61.367	33,575	D	
Common Stock	05/24/2004		M		1,500	A	\$7.31	33,575	D	
Common Stock	05/24/2004		S <sup>(1)</sup>		1,500	D	\$61.264	32,075	D	
Common Stock	05/24/2004		M		1,500	A	\$7.31	32,075	D	
Common Stock	05/24/2004		S <sup>(1)</sup>		1,500	D	\$61.2877	30,575	D	
Common Stock	05/24/2004		M		1,000	A	\$7.31	30,575	D	
Common Stock	05/24/2004		S <sup>(1)</sup>		1,000	D	\$61.32	29,575	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-tobuy) (2)	\$7.31	05/24/2004		M		1,500	(3)	12/09/2004	Common Stock 1,500	(2)	33,575	D	
Stock Option (right-tobuy) (2)	\$7.31	05/24/2004		M		1,500	(3)	12/09/2004	Common Stock 1,500	(2)	32,075	D	
Stock Option (right-tobuy) (2)	\$7.31	05/24/2004		M		1,500	(3)	12/09/2004	Common Stock 1,500	(2)	30,575	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)				6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$7.31	05/24/2004		M			1,000	(3)	12/09/2004	Common Stock	1,000	(2)	29,575	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/94.

**Remarks:**

By: Benjamin S. Harshbarger  
 For: James C. Mullen 05/26/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <b>MULLEN JAMES C</b>			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIOGEN IDEC INC [ BIIB ]</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
(Last) (First) (Middle) 14 CAMBRIDGE CENTER	<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 06/01/2004		<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
(Street) CAMBRIDGE MA 02142					<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person
(City) (State) (Zip)					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/01/2004		M		1,500	A	\$7.31	29,575	D	
Common Stock	06/01/2004		S <sup>(1)</sup>		1,500	D	\$61.82	28,075	D	
Common Stock	06/01/2004		M		1,500	A	\$7.31	28,075	D	
Common Stock	06/01/2004		S <sup>(1)</sup>		1,500	D	\$61.8707	26,575	D	
Common Stock	06/01/2004		M		1,500	A	\$7.31	26,575	D	
Common Stock	06/01/2004		S <sup>(1)</sup>		1,500	D	\$62.21	25,075	D	
Common Stock	06/01/2004		M		1,000	A	\$7.31	25,075	D	
Common Stock	06/01/2004		S <sup>(1)</sup>		1,000	D	\$62.2	24,075	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$7.31	06/01/2004		M		1,500	(3)	12/09/2004	Common Stock	1,500	(2)	28,075	D	
Stock Option (right-to-buy) (2)	\$7.31	06/01/2004		M		1,500	(3)	12/09/2004	Common Stock	1,500	(2)	26,575	D	
Stock Option (right-to-buy) (2)	\$7.31	06/01/2004		M		1,500	(3)	12/09/2004	Common Stock	1,500	(2)	25,075	D	



Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$7.31	06/01/2004		M			1,000	(3)	12/09/2004	Common Stock	1,000	(2)	24,075	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/94.

**Remarks:**

By: Benjamin S. Harshbarger  
 For: James C. Mullen

06/02/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 06/07/2004		
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b>  <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/07/2004		M		5,500	A	\$7.31	24,075	D	
Common Stock	06/07/2004		S <sup>(1)</sup>		3,000	D	\$61.85	21,075	D	
Common Stock	06/07/2004		S <sup>(1)</sup>		1,500	D	\$61.65	19,575	D	
Common Stock	06/07/2004		S <sup>(1)</sup>		1,000	D	\$61.84	18,575	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)	5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
						Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$7.31	06/07/2004		M	5,500	(3)	12/09/2004	Common Stock	5,500	(2)	18,575	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/94.

**Remarks:**

By: Benjamin S. Harshbarger 06/08/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 06/14/2004		
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b>  <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/14/2004		M		5,500	A	\$7.31	18,575	D	
Common Stock	06/14/2004		S <sup>(1)</sup>		1,500	D	\$60.0383	17,075	D	
Common Stock	06/14/2004		S <sup>(1)</sup>		1,500	D	\$60.0719	15,575	D	
Common Stock	06/14/2004		S <sup>(1)</sup>		1,500	D	\$59.96	14,075	D	
Common Stock	06/14/2004		S		1,000	D	\$60.004	13,075	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)	5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
					Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Stock Option (right-to-buy) (2)	\$7.31	06/14/2004		M			5,500	(3)	12/09/2004	Common Stock	5,500	(2)	13,075	D

**Explanation of Responses:**

- Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
- Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
- The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/94.

**Remarks:**

By: Benjamin S. Harshbarger  
For: James C. Mullen 06/15/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>			<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President		
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 06/21/2004					
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>			<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> X Form filed by One Reporting Person Form filed by More than One Reporting Person		

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/21/2004		M		4,500	A	\$7.31	13,075	D	
Common Stock	06/21/2004		S <sup>(1)</sup>		1,500	D	\$57.5215	11,575	D	
Common Stock	06/21/2004		S <sup>(1)</sup>		1,500	D	\$57.54	10,575	D	
Common Stock	06/21/2004		S <sup>(1)</sup>		1,500	D	\$57.5257	8,575	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$7.31	06/21/2004		M		4,500	(3)	12/09/2004	Common Stock	(2)	8,575	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/04.

**Remarks:**

By: Benjamin S. Harshbarger 06/23/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 06/24/2004		
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b>  <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/24/2004		M		1,000	A	\$7.31	8,575	D	
Common Stock	06/24/2004		S (1)		1,000	D	\$60.094	7,575	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$7.31	06/24/2004		M			1,000	(3)	12/09/2004	Common Stock	1,000	(2)	7,575	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/94.

**Remarks:**

By: Benjamin S. Harshbarger  
For: James C. Mullen 06/28/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 06/29/2004			
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(Street)						
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/29/2004		M		5,500	A	\$7.31	7,575	D	
Common Stock	06/29/2004		S <sup>(1)</sup>		1,500	D	\$63.132	6,075	D	
Common Stock	06/29/2004		S <sup>(1)</sup>		1,500	D	\$63.0635	4,575	D	
Common Stock	06/29/2004		S <sup>(1)</sup>		2,500	D	\$63.04	2,075	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$7.31	06/29/2004		M		5,500	(3)	12/09/2004	Common Stock	(2)	1,575	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/04.

**Remarks:**

By: Benjamin S. Harshbarger 06/30/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

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Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 06/29/2004			
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year) 06/29/2004		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(Street)	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/29/2004		M		5,500	A	\$7.31	7,575	D	
Common Stock	06/29/2004		S <sup>(1)</sup>		1,500	D	\$63.132	6,075	D	
Common Stock	06/29/2004		S <sup>(1)</sup>		1,500	D	\$63.0635	4,575	D	
Common Stock	06/29/2004		S <sup>(1)</sup>		2,500	D	\$63.04	2,075	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Common Stock (right-to-buy) (2)	\$7.31	06/29/2004		M			5,500	(3)	12/09/2004	Common Stock	5,500	(2)	2,075	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/94.

**Remarks:**

By: Benjamin S. Hrshbarger 07/08/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 07/13/2004			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	07/13/2004		M		5,500	A	\$11.73	70,175	D	
Common Stock	07/13/2004		S <sup>(1)</sup>		1,500	D	\$60.6914	68,675	D	
Common Stock	07/13/2004		S <sup>(1)</sup>		1,500	D	\$60.4817	67,175	D	
Common Stock	07/13/2004		S <sup>(1)</sup>		1,500	D	\$60.5033	65,675	D	
Common Stock	07/13/2004		S <sup>(1)</sup>		1,000	D	\$60.7	64,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$11.73	07/13/2004		M		5,500	(3)	09/22/2005	Common Stock 5,500	(2)	64,675	D	

**Explanation of Responses:**

- Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
- Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
- The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/05.

**Remarks:**

By: Benjamin S. Harshbarger 07/15/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 07/19/2004			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	07/19/2004		M		4,500	A	\$11.73	64,675	D	
Common Stock	07/19/2004		S <sup>(1)</sup>		1,500	D	\$57.918	63,175	D	
Common Stock	07/19/2004		S <sup>(1)</sup>		1,500	D	\$57.8993	61,675	D	
Common Stock	07/19/2004		S <sup>(1)</sup>		1,500	D	\$57.9553	60,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	07/13/2004		M			4,500	(3)	09/22/2005	Common Stock	4,500	(2)	60,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger 07/20/2004

For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)	<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>	<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
	<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 07/26/2004	
<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	07/26/2004		M		4,500	A	\$11.73	60,175	D	
Common Stock	07/26/2004		S <sup>(1)</sup>		1,500	D	\$53.3503	58,675	D	
Common Stock	07/26/2004		S <sup>(1)</sup>		1,500	D	\$53.4382	57,175	D	
Common Stock	07/19/2004		S <sup>(1)</sup>		1,500	D	\$53.506	55,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares			
Stock Option (right-to-buy) (2)	\$11.73	07/26/2004		M			4,500	(3)	09/22/2005	Common Stock	4,500	(2)	55,675	D

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/05.

**Remarks:**

By: Benjamin S. Harshbarger 07/27/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 07/30/2004			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	07/30/2004		M		1,000	A	\$11.73	55,675	D	
Common Stock	07/30/2004		S <sup>(1)</sup>		1,000	D	\$59.8592	54,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$11.73	07/30/2004		M		1,000	(3)	09/22/2005	Common Stock 1,000	(2)	54,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger 08/02/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

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Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 08/02/2004			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
			<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person		

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/02/2004		M		4,500	A	\$11.73	54,675	D	
Common Stock	08/02/2004		S <sup>(1)</sup>		1,500	D	\$59.0081	53,175	D	
Common Stock	08/02/2004		S <sup>(1)</sup>		1,500	D	\$58.61	51,675	D	
Common Stock	08/02/2004		S <sup>(1)</sup>		1,500	D	\$58.2	50,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$11.73	08/02/2004		M			4,500	(3)	09/22/2005	Common Stock	4,500	(2)	50,175	D

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger 08/04/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>			<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President		
(Last) (First) (Middle) 14 CAMBRIDGE CENTER			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 08/10/2004			<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person		
(Street) CAMBRIDGE MA 02142			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>					
(City) (State) (Zip)								

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/10/2004		M		4,500	A	\$11.73	50,175	D	
Common Stock	08/10/2004		S <sup>(1)</sup>		1,500	D	\$55.8953	48,675	D	
Common Stock	08/10/2004		S <sup>(1)</sup>		1,500	D	\$55.9058	47,175	D	
Common Stock	08/10/2004		S <sup>(1)</sup>		1,500	D	\$55.906	45,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	08/10/2004		M			4,500	(3)	09/22/2005	Common Stock	4,500	(2)	45,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/05.

**Remarks:**

By: Benjamin S. Harshbarger 08/11/2004  
 For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.



SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 08/16/2004			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person <input type="checkbox"/> Form filed by More than One Reporting Person					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/16/2004		M		4,500	A	\$11.73	45,675	D	
Common Stock	08/16/2004		S <sup>(1)</sup>		4,500	D	\$58.42	41,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)	5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)	
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	08/16/2004		M			4,500	(3)	09/22/2005	Common Stock	4,500	(2)	41,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger  
For: James C. Mullen

08/18/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

**Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.**

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>			<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President		
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 08/18/2004					
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>			<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person		

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/18/2004		M		1,000	A	\$11.73	41,175	D	
Common Stock	08/18/2004		S <sup>(1)</sup>		1,000	D	\$60	40,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	08/18/2004		M			1,000	(3)	09/22/2005	Common Stock	1,000	(2)	40,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.  
 2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).  
 3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger 08/19/2004  
 For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 08/23/2004			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/23/2004		M		4,500	A	\$11.73	40,175	D	
Common Stock	08/23/2004		S <sup>(1)</sup>		3,000	D	\$59.6073	37,175	D	
Common Stock	08/23/2004		S <sup>(1)</sup>		1,500	D	\$59.6134	35,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$11.73	08/23/2004		M		4,500	(3)	09/22/2005	Common Stock 4,500	(2)	35,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/05.

**Remarks:**

By: Benjamin S. Harshbarger 08/24/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 08/25/2004			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/25/2004		M		1,000	A	\$11.73	35,675	D	
Common Stock	08/25/2004		S <sup>(1)</sup>		1,000	D	\$60.003	34,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	08/25/2004		M			1,000	(3)	09/22/2005	Common Stock	1,000	(2)	34,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.  
 2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).  
 3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger 08/27/2004  
 For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person*			2. Issuer Name and Ticker or Trading Symbol		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)	
MULLEN JAMES C			BIOGEN IDEC INC [ BIIB ]		<input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year)			
14	CAMBRIDGE	CENTER	08/30/2004			
(Street)			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line)	
CAMBRIDGE	MA	02142			<input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/30/2004		M		5,500	A	\$11.73	34,675	D	
Common Stock	08/30/2004		S <sup>(1)</sup>		1,500	D	\$59.3867	33,175	D	
Common Stock	08/30/2004		S <sup>(1)</sup>		1,000	D	\$60.24	32,175	D	
Common Stock	08/30/2004		S <sup>(1)</sup>		1,500	D	\$59.4206	30,675	D	
Common Stock	08/30/2004		S <sup>(1)</sup>		1,500	D	\$59.4754	29,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	08/30/2004		M			5,500	(3)	09/22/2005	Common Stock	5,500	(2)	29,175	D	

**Explanation of Responses:**

- Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
- Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
- The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger 08/31/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 09/07/2004		
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b>  <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	09/07/2004		M		5,500	A	\$11.73	29,175	D	
Common Stock	09/07/2004		S <sup>(1)</sup>		1,500	D	\$61.5	27,675	D	
Common Stock	09/07/2004		S <sup>(1)</sup>		1,500	D	\$61.31	26,175	D	
Common Stock	09/07/2004		S <sup>(1)</sup>		1,500	D	\$61.49	24,675	D	
Common Stock	09/07/2004		S <sup>(1)</sup>		1,000	D	\$60.7	23,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$11.73	09/07/2004		M		5,500	(3)	09/22/2005	Common Stock 5,500	(2)	23,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.  
 2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).  
 3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/05.

**Remarks:**

By: Benjamin S. Harshbarger 09/08/2004  
 For: James C. Mullen  
 \*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable)  <input type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 09/13/2004			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	09/13/2004		M		5,500	A	\$11.73	23,675	D	
Common Stock	09/13/2004		S <sup>(1)</sup>		1,500	D	\$61.77	22,175	D	
Common Stock	09/13/2004		S <sup>(1)</sup>		1,500	D	\$61.7434	20,675	D	
Common Stock	09/13/2004		S <sup>(1)</sup>		1,500	D	\$61.86	19,175	D	
Common Stock	09/13/2004		S <sup>(1)</sup>		1,000	D	\$61.8	18,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy)	\$11.73	09/13/2004		M			5,500	( <sup>2</sup> )	09/22/2005	Common Stock	( <sup>3</sup> )	18,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.
3. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).

**Remarks:**

By: Benjamin S. Harshbarger 09/15/2004  
 For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <b>MULLEN JAMES C</b>			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIAGEN IDEC INC [ BIIB ]</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input type="checkbox"/> Director <span style="float: right;">10% Owner</span> <input checked="" type="checkbox"/> Officer (give title below) <span style="float: right;">Other (specify below)</span> <div style="text-align: center;">CEO &amp; President</div>	
(Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 09/20/2004		<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person <input type="checkbox"/> Form filed by More than One Reporting Person	
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>			

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	09/20/2004		M		5,500	A	\$11.73	18,175	D	
Common Stock	09/20/2004		S <sup>(1)</sup>		1,500	D	\$62.18	16,675	D	
Common Stock	09/20/2004		S <sup>(1)</sup>		1,500	D	\$62.37	15,175	D	
Common Stock	09/20/2004		S <sup>(1)</sup>		1,500	D	\$62.15	13,675	D	
Common Stock	09/20/2004		S <sup>(1)</sup>		1,000	D	\$61.58	12,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	09/20/2004		M			5,500	(3)	09/22/2005	Common Stock	5,500	(2)	12,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger; 09/21/2004  
 For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <b>MULLEN JAMES C</b>			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIOM IDEC INC [ BIIB ]</b>			<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director <span style="float: right;">10% Owner</span> <input checked="" type="checkbox"/> Officer (give title below) <span style="float: right;">Other (specify below)</span> <div style="text-align: center;">CEO &amp; President</div>		
(Last) (First) (Middle) 14 CAMBRIDGE CENTER			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 09/27/2004					
(Street) CAMBRIDGE MA 02142			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>			<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person		
(City) (State) (Zip)								

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	09/27/2004		M		5,500	A	\$11.73	12,675	D	
Common Stock	09/27/2004		S <sup>(1)</sup>		4,500	D	\$59.5	8,175	D	
Common Stock	09/27/2004		S <sup>(1)</sup>		1,000	D	\$60	7,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	09/27/2004		M			5,500	(3)	09/22/2005	Common Stock	5,500	(2)	7,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger; 09/29/2004  
 For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 10/04/2004			
14 CAMBRIDGE CENTER						
(Street)			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	10/04/2004		M		5,500	A	\$11.73	7,175	D	
Common Stock	10/04/2004		S <sup>(1)</sup>		1,500	D	\$62.482	5,675	D	
Common Stock	10/04/2004		S <sup>(1)</sup>		1,500	D	\$62.8454	4,175	D	
Common Stock	10/04/2004		S <sup>(1)</sup>		1,500	D	\$62.772	2,675	D	
Common Stock	10/04/2004		S <sup>(1)</sup>		1,000	D	\$62.38	1,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$11.73	10/04/2004		M			5,500	(3)	09/22/2005	Common Stock	5,500	(2)	1,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.

**Remarks:**

By: Benjamin S. Harshbarger; 10/05/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

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\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President	
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 10/11/2004			
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	10/11/2004		M		1,675	A	\$11.73	1,675	D	
Common Stock	10/11/2004		S <sup>(1)</sup>		1,500	D	\$60.12	175	D	
Common Stock	10/11/2004		S <sup>(1)</sup>		175	D	\$60.33	0	D	
Common Stock	10/11/2004		M		3,825	A	\$16.9	46,000	D	
Common Stock	10/11/2004		S <sup>(1)</sup>		1,325	D	\$60.33	44,675	D	
Common Stock	10/11/2004		S <sup>(1)</sup>		1,500	D	\$59.95	43,175	D	
Common Stock	10/11/2004		S <sup>(1)</sup>		1,000	D	\$60	42,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$11.73	10/11/2004		M		1,675	(3)	09/22/2005	Common Stock	(2)	0	D	
Stock Option (right-to-buy) (2)	\$16.9	10/11/2004		M		3,825	(4)	12/06/2006	Common Stock	(2)	42,175	D	

**Explanation of Responses:**

- Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
- Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
- The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 09/22/95.
- The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 10/13/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.



\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIAGEN IDEC INC [ BIIB ]</u>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 10/18/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	10/18/2004		M		3,825	A	\$16.9	42,175	D	
Common Stock	10/18/2004		S <sup>(1)</sup>		1,500	D	\$57.5	40,675	D	
Common Stock	10/18/2004		S <sup>(1)</sup>		1,500	D	\$58.0487	39,175	D	
Common Stock	10/18/2004		S <sup>(1)</sup>		1,500	D	\$57.8073	37,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)	5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)			
															Date Exercisable
Stock Option (right-to-buy) (2)	\$16.9	10/11/2004		M			4,500	(3)	12/06/2006	Common Stock	4,500	(2)	37,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 10/19/2004  
 For: James C. Mullen  
 \*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 10/18/2004			
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year) 10/20/2004			
(Street)	MA	02142			6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	10/18/2004		M		4,500	A	\$16.9	42,175	D	
Common Stock	10/18/2004		S <sup>(1)</sup>		1,500	D	\$57.5	40,675	D	
Common Stock	10/18/2004		S <sup>(1)</sup>		1,500	D	\$58.0487	39,175	D	
Common Stock	10/18/2004		S <sup>(1)</sup>		1,500	D	\$57.8073	37,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$16.9	10/18/2004		M			4,500	(3)	12/06/2006	Common Stock	4,500	(2)	37,675	D

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

This Form 4A amends the Form 4 filed on 10/20/2004.

By: Benjamin S. Harshbarger; 10/26/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 10/25/2004			
14 CAMBRIDGE CENTER						
(Street)			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	10/25/2004		M		4,500	A	\$16.9	37,675	D	
Common Stock	10/25/2004		S <sup>(1)</sup>		1,500	D	\$55.882	36,175	D	
Common Stock	10/25/2004		S <sup>(1)</sup>		1,500	D	\$56.09	34,675	D	
Common Stock	10/25/2004		S <sup>(1)</sup>		1,500	D	\$55.8689	33,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$16.9	10/25/2004		M			4,500	(3)	12/06/2006	CCommon Stock	4,500	(2)	33,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 10/26/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <u>MULLEN JAMES C</u>			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIAGEN IDEC INC [ BIIB ]</u>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President
(Last) (First) (Middle) 14 CAMBRIDGE CENTER	<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 10/28/2004		<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
(Street) CAMBRIDGE MA 02142					<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person
(City) (State) (Zip)					

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	10/28/2004		M		1,000	A	\$16.9	33,175	D	
Common Stock	10/28/2004		S <sup>(1)</sup>		1,000	D	\$60	32,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)	5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
					Code	V	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) <sup>(2)</sup>	\$16.9	10/28/2004		M				12/06/2006	Common Stock	1,000	(2)	32,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger;  
 For: James C. Mullen

11/01/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 11/01/2004			
14 CAMBRIDGE CENTER						
(Street) CAMBRIDGE MA 02142			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(City) (State) (Zip)						

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	11/01/2004		M		4,500	A	\$16.9	32,175	D	
Common Stock	11/01/2004		S <sup>(1)</sup>		1,500	D	\$58	30,675	D	
Common Stock	11/01/2004		S <sup>(1)</sup>		1,500	D	\$57.7937	29,175	D	
Common Stock	11/01/2004		S <sup>(1)</sup>		1,500	D	\$58.2706	27,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$16.9	11/01/2004		M			4,500	(3)	12/06/2006	Common Stock	4,500	(2)	27,675	D

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 11/02/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIAGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 11/03/2004			
14 CAMBRIDGE CENTER						
(Street) CAMBRIDGE MA 02142			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	11/03/2004		M		1,000	A	\$16.9	27,675	D	
Common Stock	11/03/2004		S <sup>(1)</sup>		1,000	D	\$60.002	26,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) <sup>(2)</sup>	\$16.9	11/03/2004		M			1,000	<sup>(3)</sup>	12/06/2006	Common Stock	1,000	<sup>(2)</sup>	26,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 11/04/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D. C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <u>MULLEN JAMES C</u>			2. Issuer Name and Ticker or Trading Symbol <u>BIOGEN IDEC INC [ BIIB ]</u>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 11/08/2004			
14 CAMBRIDGE CENTER						
(Street) CAMBRIDGE MA 02142			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	11/08/2004		M		5,500	A	\$16.9	26,675	D	
Common Stock	11/08/2004		S <sup>(1)</sup>		1,500	D	\$61.014	25,175	D	
Common Stock	11/08/2004		S <sup>(1)</sup>		1,500	D	\$61.0613	23,675	D	
Common Stock	11/08/2004		S <sup>(1)</sup>		1,500	D	\$61.2389	22,175	D	
Common Stock	11/08/2004		S <sup>(1)</sup>		1,000	D	\$61.547	21,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$16.9	11/08/2004		M			5,500	(3)	12/06/2006	Common Stock	5,500	(2)	21,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 11/09/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 11/15/2004		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	11/15/2004		M		4,500	A	\$16.9	21,175	D	
Common Stock	11/15/2004		S <sup>(1)</sup>		1,500	D	\$58.67	19,675	D	
Common Stock	11/15/2004		S <sup>(1)</sup>		1,500	D	\$58.8036	18,175	D	
Common Stock	11/15/2004		S <sup>(1)</sup>		1,500	D	\$58.6933	16,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$16.9	11/15/2004		M			4,500	(3)	12/06/2006	Common Stock	4,500	(2)	16,675	D

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 11/17/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 11/22/2004			
14 CAMBRIDGE CENTER						
(Street)			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	11/22/2004		M		4,500	A	\$16.9	16,675	D	
Common Stock	11/22/2004		S <sup>(1)</sup>		1,500	D	\$58.67	15,175	D	
Common Stock	11/22/2004		S <sup>(1)</sup>		1,500	D	\$58.8036	13,675	D	
Common Stock	11/22/2004		S <sup>(1)</sup>		1,500	D	\$58.6933	12,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) <sup>(2)</sup>	\$16.9	11/22/2004		M			4,500	<sup>(3)</sup>	12/06/2006	Common Stock	<sup>(2)</sup>	12,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 11/23/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 11/29/2004		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	11/29/2004		M		4,500	A	\$16.9	12,175	D	
Common Stock	11/29/2004		S <sup>(1)</sup>		1,500	D	\$58.7519	10,675	D	
Common Stock	11/29/2004		S <sup>(1)</sup>		1,500	D	\$58.5267	9,175	D	
Common Stock	11/29/2004		S <sup>(1)</sup>		1,500	D	\$58.794	7,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) <sup>(2)</sup>	\$16.9	11/29/2004		M			4,500	<sup>(3)</sup>	12/06/2006	Common Stock	<sup>(2)</sup>	7,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 12/01/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see instruction 4 (b)(v).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 12/02/2004			
14 CAMBRIDGE CENTER						
(Street) CAMBRIDGE MA 02142			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	12/02/2004		M		1,000	A	\$16.9	7,675	D	
Common Stock	12/02/2004		S <sup>(1)</sup>		1,000	D	\$60	6,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$16.9	12/02/2004		M			1,000	(3)	12/06/2006	Common Stock 1,000	(2)	6,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 12/03/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 12/06/2004			
14 CAMBRIDGE CENTER						
(Street) CAMBRIDGE MA 02142			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	12/06/2004		M		5,500	A	\$16.9	6,675	D	
Common Stock	12/06/2004		S <sup>(1)</sup>		1,500	D	\$60.84	5,175	D	
Common Stock	12/06/2004		S <sup>(1)</sup>		1,500	D	\$61.498	3,675	D	
Common Stock	12/06/2004		S <sup>(1)</sup>		1,500	D	\$60.6766	2,175	D	
Common Stock	12/06/2004		S <sup>(1)</sup>		1,000	D	\$61.2904	1,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$16.9	12/06/2004		M			5,500	(3)	12/06/2006	Common Stock	5,500	(2)	1,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.

**Remarks:**

By: Benjamin S. Harshbarger; 12/08/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person</b> <b>MULLEN JAMES C</b>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIOGEN IDEC INC [ BIIB ]</b>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 12/13/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) CEO & President  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	12/13/2004		M		1,175	A	\$16.9	1,175	D	
Common Stock	12/13/2004		S <sup>(1)</sup>		1,175	D	\$65.7667	0	D	
Common Stock	12/13/2004		M		4,325	A	\$15.54	46,000	D	
Common Stock	12/13/2004		S <sup>(1)</sup>		325	D	\$65.7667	45,675	D	
Common Stock	12/13/2004		S <sup>(1)</sup>		1,000	D	\$65.0119	44,675	D	
Common Stock	12/13/2004		S <sup>(1)</sup>		1,500	D	\$65.6947	43,175	D	
Common Stock	12/13/2004		S <sup>(1)</sup>		1,500	D	\$65.68	41,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$16.9	12/13/2004		M			1,175	(3)	12/06/2006	Common Stock	1,175	(2)	0	D	
Stock Option (right-to-buy) (2)	\$15.54	12/13/2004		S			4,325	(4)	12/12/2007	Common Stock	4,325	(2)	41,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/06/96.
4. The stock option became exercisable in five (5) equal annual installments, commencing one year after the grant date of 12/12/97.

**Remarks:**

By: Benjamin S. Harshbarger; 12/16/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).



**\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).**

**Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.**

**Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.**

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 12/20/2004		
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)		
(Street)	(City)	(State)	(Zip)	6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	12/20/2004		M		5,500	A	\$15.54	41,675	D	
Common Stock	12/20/2004		S <sup>(1)</sup>		1,000	D	\$65.0443	40,675	D	
Common Stock	12/20/2004		S <sup>(1)</sup>		1,500	D	\$65.0108	39,175	D	
Common Stock	12/20/2004		S <sup>(1)</sup>		1,500	D	\$65.0226	37,675	D	
Common Stock	12/20/2004		S <sup>(1)</sup>		1,500	D	\$65.008	36,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$15.54	12/20/2004		S			5,500	(3)	12/12/2007	Common Stock	(2)	36,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in five (5) equal annual installments, commencing one year after the grant date of 12/12/97.

**Remarks:**

By: Benjamin S. Harshbarger; 12/21/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIAGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 12/27/2004			
14 CAMBRIDGE CENTER						
(Street)			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	12/27/2004		M		5,500	A	\$15.54	36,175	D	
Common Stock	12/27/2004		S <sup>(1)</sup>		1,500	D	\$65.9093	34,675	D	
Common Stock	12/27/2004		S <sup>(1)</sup>		1,000	D	\$65.972	33,675	D	
Common Stock	12/27/2004		S <sup>(1)</sup>		1,500	D	\$65.898	32,175	D	
Common Stock	12/27/2004		S <sup>(1)</sup>		1,500	D	\$66.394	30,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) <sup>(2)</sup>	\$15.54	12/27/2004		S			5,500	<sup>(3)</sup>	12/12/2007	Common Stock	5,500	<sup>(2)</sup>	30,675	D

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in five (5) equal annual installments, commencing one year after the grant date of 12/12/97.

**Remarks:**

By: Benjamin S. Harshbarger; 12/28/2004  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIAGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 01/03/2005		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	(City)	(State)	(Zip)			

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	01/03/2005		M		5,500	A	\$15.54	30,675	D	
Common Stock	01/03/2005		S <sup>(1)</sup>		1,500	D	\$67.1	29,175	D	
Common Stock	01/03/2005		S <sup>(1)</sup>		1,500	D	\$67	27,675	D	
Common Stock	01/03/2005		S <sup>(1)</sup>		1,000	D	\$67.55	26,675	D	
Common Stock	01/03/2005		S <sup>(1)</sup>		1,500	D	\$67.6917	25,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) <sup>(2)</sup>	\$15.54	01/03/2005		S		5,500	<sup>(3)</sup>	12/12/2007	Common Stock	<sup>(2)</sup>	25,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in five (5) equal annual installments, commencing one year after the grant date of 12/12/97.

**Remarks:**

By: Benjamin S. Harshbarger; 01/04/2005  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 01/10/2005			
14 CAMBRIDGE CENTER						
(Street)			4. If Amendment, Date of Original Filed (Month/Day/Year)		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	01/10/2005		M		5,500	A	\$15.54	25,175	D	
Common Stock	01/10/2005		S <sup>(1)</sup>		1,500	D	\$66.902	23,675	D	
Common Stock	01/10/2005		S <sup>(1)</sup>		1,500	D	\$65.9438	22,175	D	
Common Stock	01/10/2005		S <sup>(1)</sup>		1,000	D	\$66.23	21,175	D	
Common Stock	01/10/2005		S <sup>(1)</sup>		1,500	D	\$66.5838	19,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) <sup>(2)</sup>	\$15.54	01/10/2005		S			5,500	<sup>(3)</sup>	12/12/2007	Common Stock	5,500	<sup>(2)</sup>	19,675	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in five (5) equal annual installments, commencing one year after the grant date of 12/12/97.

**Remarks:**

By: Benjamin S. Harshbarger; 01/12/2005  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>			5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President		
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 01/18/2005					
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person		
(Street)								
CAMBRIDGE	MA	02142						
(City)	(State)	(Zip)						

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	01/18/2005		M		5,500	A	\$15.54	19,675	D	
Common Stock	01/18/2005		S <sup>(1)</sup>		1,500	D	\$68.0469	18,175	D	
Common Stock	01/18/2005		S <sup>(1)</sup>		1,500	D	\$67.7667	16,675	D	
Common Stock	01/18/2005		S <sup>(1)</sup>		1,500	D	\$67.86	15,175	D	
Common Stock	01/18/2005		S <sup>(1)</sup>		1,000	D	\$67.4	14,175	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) <sup>(2)</sup>	\$15.54	01/18/2005		S		5,500	<sup>(3)</sup>	12/12/2007	Common Stock	<sup>(2)</sup>	14,175	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in five (5) equal annual installments, commencing one year after the grant date of 12/12/97.

**Remarks:**

By: Benjamin S. Harshbarger;  
For: James C. Mullen

01/20/2005

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>MULLEN JAMES C</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  X Director 10% Owner X Officer (give title below) Other (specify below) CEO & President	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 01/24/2005		6. Individual or Joint/Group Filing (Check Applicable Line)  X Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)						
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	01/24/2005		M		5,500	A	\$15.54	14,175	D	
Common Stock	01/24/2005		S <sup>(1)</sup>		1,500	D	\$64.04	12,675	D	
Common Stock	01/24/2005		S <sup>(1)</sup>		1,500	D	\$64.55	11,175	D	
Common Stock	01/24/2005		S <sup>(1)</sup>		1,500	D	\$62.968	9,675	D	
Common Stock	01/24/2005		S <sup>(1)</sup>		1,000	D	\$64.36	8,675	D	
Common Stock								94,252	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$15.54	01/24/2005		S		5,500	(3)	12/12/2007	Common Stock	5,500	(2)	8,675	D

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. The stock option became exercisable in five (5) equal annual installments, commencing one year after the grant date of 12/12/97.

**Remarks:**

By: Benjamin S. Harshbarger; 01/26/2005  
For: James C. Mullen

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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## **EXHIBIT 19**

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>ADELMAN BURT A</u>  (Last) (First) (Middle) BIOGEN INC LEGAL DEPARTMENT 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)	<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 03/29/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>	<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director 10% Owner X Officer (give title below) Other (specify below) Executive VP Development  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> X Form filed by One Reporting Person Form filed by More than One Reporting Person
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	03/29/2004		M		4,370	A	\$7.31	16,639	D	
Common Stock	03/29/2004		S <sup>(1)</sup>		4,370	D	\$53.37	12,269	D	
Common Stock	03/29/2004		M		8,222	A	\$9.67	20,491	D	
Common Stock	03/29/2004		S <sup>(1)</sup>		8,222	D	\$53.37	12,269	D	
Common Stock								8,009	I	By GRATs

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
1985 NQ Stock Option	\$7.31	03/29/2004		M			4,370	(3)	12/09/2004	Common Stock	4,370	(2)	0	D	
1985 NQ Stock Option	\$9.67	03/29/2004		M			8,222	(4)	06/22/2005	Common Stock	8,222	(2)	37,778	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under Issuer's Employee Stock Option Plan, in an exempt transaction under SEC rule 16b-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 12/09/94.
4. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 06/22/95.

By: Benjamin S. Harshbarger 03/31/2004  
For: Burt A. Adelman

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

**Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.**

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <u>ADELMAN BURT A</u>			2. Issuer Name and Ticker or Trading Symbol <u>BIOGEN IDEC INC [ BIIB ]</u>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) EVP, Development	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 05/05/2004		6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	05/05/2004		M		4,200	A	\$12.91	69,000	D	
Common Stock	05/05/2004		S		4,200	D	\$58.26	64,800	D	
Common Stock	05/05/2004		M		500	A	\$12.91	64,800	D	
Common Stock	05/05/2004		S		500	D	\$58.28	64,300	D	
Common Stock	05/05/2004		M		2,900	A	\$12.91	64,300	D	
Common Stock	05/05/2004		S		2,900	D	\$58.29	61,400	D	
Common Stock	05/05/2004		M		1,100	A	\$12.91	61,400	D	
Common Stock	05/05/2004		S		1,100	D	\$58.31	60,300	D	
Common Stock	05/05/2004		M		1,300	A	\$12.91	60,300	D	
Common Stock	05/05/2004		S		1,300	D	\$58.3	59,000	D	
Common Stock								12,269	D	
Common Stock								8,009	I	by GRATs

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (1)	\$12.91	05/05/2004		M			4,200	(2)	04/18/2006	Common Stock	4,200	(1)	64,800	D	
Stock Option (right-to-buy) (1)	\$12.91	05/05/2004		M			500	(2)	04/18/2006	Common Stock	500	(1)	64,300	D	
Stock Option (right-to-buy) (1)	\$12.91	05/05/2004		M			2,900	(2)	04/18/2006	Common Stock	2,900	(1)	61,400	D	
Stock Option (right-to-buy) (1)	\$12.91	05/05/2004		M			1,100	(2)	04/18/2006	Common Stock	1,100	(1)	60,300	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (1)	\$12.91	05/05/2004		M			1,300	(2)	04/18/2006	Common Stock	1,300	(1)	59,000	D	

**Explanation of Responses:**

1. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16-3(d).
2. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 04/18/96.

**Remarks:**

By: Benjamin S. Harshbarger      05/05/2006  
 For: Burt A. Adelman  
 \*\* Signature of Reporting Person      Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <b>ADELMAN BURT A</b>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIOGEN IDEC INC [ BIIB ]</b>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 06/28/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) EVP, Development  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/28/2004		M		12,593	A	\$9.67	37,778	D	
Common Stock	06/28/2004		S		12,593	D	\$63	25,185	D	
Common Stock								12,269	D	
Common Stock								8,009	I	by GRATs

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$12.91	06/28/2004		M		12,593	(3)	06/22/2005	Common Stock	(2)	25,185	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 06/22/95.

**Remarks:**

By: Benjamin S. Harshbarger  
 For: Burt A. Adelman

06/29/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**
☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person</b> <u>ADELMAN BURT A</u>  (Last) (First) (Middle) 14 CAMBRIDGE CENTER  (Street) CAMBRIDGE MA 02142  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u> BIOGEN IDEC INC [ BIIB ]</u>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 09/27/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) EVP, Development  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	09/27/2004		M		12,592	A	\$9.67	25,185	D	
Common Stock	09/27/2004		S (1)		12,592	D	\$59.21	12,593	D	
Common Stock								12,269	D	
Common Stock								8,009	I	by GRATs

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$9.67	09/27/2004		M		12,592	(3)	06/22/2005	Common Stock	(2)	12,593	D	

**Explanation of Responses:**

- Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
- Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16-3(d).
- The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 06/22/95.

**Remarks:**

By: Benjamin S. Harshbarger 09/29/2004  
 For: Burt A. Adelman  
 \*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person* <u>ADELMAN BURT A</u>			2. Issuer Name and Ticker or Trading Symbol <u>BIAGEN IDEC INC [ BIIB ]</u>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) EVP, Development	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 12/27/2004		6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	CAMBRIDGE MA 02142					
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	12/27/2004		M		12,593	A	\$9.67	12,593	D	
Common Stock	12/27/2004		S <sup>(1)</sup>		12,593	D	\$65.1822	0	D	
Common Stock								12,269	D	
Common Stock								8,009	I	by GRATs

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
Stock Option (right-to-buy) <sup>(2)</sup>	\$9.67	12/27/2004		M		12,593	<sup>(3)</sup>	06/22/2005	Common Stock	<sup>(2)</sup>	0	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 06/22/05.

**Remarks:**

By: Benjamin S. Harshbarger 12/28/2004  
For: Burt A. Adelman

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <b>ADELMAN BURT A</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) EVP, Development	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 01/03/2005		6. Individual or Joint/Group Filing (Check Applicable Line)  <input checked="" type="checkbox"/> Form filed by One Reporting Person  Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	CAMBRIDGE MA 02142					
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	01/03/2005		M		20,500	A	\$12.91	59,000	D	
Common Stock	01/03/2005		S <sup>(1)</sup>		5,000	D	\$67.21	54,000	D	
Common Stock	01/03/2005		S <sup>(1)</sup>		5,500	D	\$67.11	48,500	D	
Common Stock	01/03/2005		S <sup>(1)</sup>		10,000	D	\$66.9	38,500	D	
Common Stock								12,269	D	
Common Stock								8,009	I	by GRATs

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
Stock Option (right-to-buy) (2)	\$12.91	01/03/2005		M			20,500	(1)	04/18/2006	Common Stock	(2)	0	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans. in an exempt transaction under SEC rule 16-3(d).
3. The stock option became exercisable in six (6) equal annual installments, commencing one year after the grant date of 04/18/96.

**Remarks:**

By: Benjamin S. Harshbarger  
For: Burt A. Adelman 01/04/2005  
\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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## **EXHIBIT 20**

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>ROHN WILLIAM R</u>  (Last) (First) (Middle) C/O CERUS CORP 2411 STENWELL DRIVE  (Street) CONCORD CA 94520  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOMED IDEC INC [ BIIB ]</u>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 02/20/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director 10% Owner X Officer (give title below) Other (specify below) Exec VP & COO  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> X Form filed by One Reporting Person Form filed by More than One Reporting Person	
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	02/18/2004		M		18,100	A	\$6.1875	37,725	D	
Common Stock	02/18/2004		S <sup>(1)</sup>		18,100	D	\$51.9	19,625	D	
Common Stock	02/18/2004		M		4,400	A	\$6.1875	24,025	D	
Common Stock	02/18/2004		S <sup>(1)</sup>		4,400	D	\$51.91	19,625	D	
Common Stock	02/18/2004		M		500	A	\$6.1875	20,125	D	
Common Stock	02/18/2004		S <sup>(1)</sup>		500	D	\$51.938	19,625	D	
Common Stock	02/18/2004		M		1,500	A	\$6.1875	21,125	D	
Common Stock	02/18/2004		S <sup>(1)</sup>		1,500	D	\$51.92	19,625	D	
Common Stock	02/18/2004		M		500	A	\$6.1875	20,125	D	
Common Stock	02/18/2004		S <sup>(1)</sup>		500	D	\$51.94	19,625	D	
Common Stock								6,000	I	by Spouse
Common Stock <sup>(2)</sup>								377,388	I	by Trust

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	02/18/2004		M			18,100	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	18,100	<sup>(2)</sup>	80,175	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	02/18/2004		M			4,400	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	4,400	<sup>(2)</sup>	75,775	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	02/18/2004		M			500	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	500	(2)	75,275	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	02/18/2004		M			1,500	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	1,500	(2)	73,775	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	02/18/2004		M			500	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	500	(2)	73,275	D	

**Explanation of Responses:**

1. Represents sale by William Rohn pursuant to a qualified written selling plan under SEC rule 10b5-1.
2. Granted under Issuer's Employee Stock Option Plan, in an exempt transaction under SEC rule 16b-3(d).
3. Option became exercisable as to 25% of the optioned shares on 4/15/99 and as to the balance of the shares in 36 equal monthly installments thereafter.

By: Pamela A. Blas For:William R. Rohn02/20/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16, Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person* <b>ROHN WILLIAM R</b>	2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  Director 10% Owner X Officer (give title below) Other (specify below) Exec VP & COO
(Last) (First) (Middle) C/O CERUS CORP 2411 STENWELL DRIVE	3. Date of Earliest Transaction (Month/Day/Year) 03/02/2004	
(Street) CONCORD CA 94520  (City) (State) (Zip)	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	03/02/2004		M		2,200	A	\$7.7188	21,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		2,200	D	\$55.73	19,625	D	
Common Stock	03/02/2004		M		4,700	A	\$7.7188	24,325	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		4,700	D	\$55.75	19,625	D	
Common Stock	03/02/2004		M		1,000	A	\$6.1875	20,625	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		1,000	D	\$55.64	19,625	D	
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.641	19,625	D	
Common Stock	03/02/2004		M		17,900	A	\$6.1875	37,525	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		17,900	D	\$55.65	19,625	D	
Common Stock	03/02/2004		M		1,800	A	\$6.1875	21,425	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		1,800	D	\$55.66	19,625	D	
Common Stock	03/02/2004		M		1,700	A	\$6.1875	21,325	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		1,700	D	\$55.67	19,625	D	
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.671	19,625	D	
Common Stock	03/02/2004		M		5,200	A	\$6.1875	24,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		5,200	D	\$55.68	19,625	D	
Common Stock	03/02/2004		M		200	A	\$7.7188	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.761	19,625	D	
Common Stock	03/02/2004		M		6,600	A	\$7.7188	26,225	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		6,600	D	\$55.91	19,625	D	
Common Stock	03/02/2004		M		4,900	A	\$7.7188	24,525	D	

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	03/02/2004		S <sup>(1)</sup>		4,900	D	\$55.93	19,625	D	
Common Stock	03/02/2004		M		1,300	A	\$7.7188	20,925	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		1,300	D	\$55.94	19,625	D	
Common Stock	03/02/2004		M		8,000	A	\$6.1875	27,625	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		8,000	D	\$55.5	19,625	D	
Common Stock	03/02/2004		M		4,300	A	\$6.1875	23,925	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		4,300	D	\$55.51	19,625	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
						(A) (D)			Title Amount or Number of Shares				

**Explanation of Responses:**

1. Represents sale by William Rohn pursuant to a trading plan intended to comply with SEC rule 10b5-1.

By: Pamela A. Blas For:  
William R. Rohn

03/04/2004

\*\* Signature of Reporting  
Person

Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.



SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

<b>1. Name and Address of Reporting Person*</b> <u>ROHN WILLIAM R</u>  (Last) (First) (Middle) C/O CERUS CORP 2411 STENWELL DRIVE  (Street) CONCORD CA 94520  (City) (State) (Zip)	<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 03/02/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>	<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director 10% Owner X Officer (give title below) Other (specify below) Exec VP & COO  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> X Form filed by One Reporting Person Form filed by More than One Reporting Person
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.511	19,625	D	
Common Stock	03/02/2004		M		500	A	\$6.1875	20,125	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		500	D	\$55.516	19,625	D	
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.58	19,625	D	
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.581	19,625	D	
Common Stock	03/02/2004		M		500	A	\$6.1875	20,125	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		500	D	\$55.59	19,625	D	
Common Stock	03/02/2004		M		9,800	A	\$6.1875	29,425	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		9,800	D	\$55.6	19,625	D	
Common Stock	03/02/2004		M		300	A	\$6.1875	19,925	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		300	D	\$55.61	19,625	D	
Common Stock	03/02/2004		M		600	A	\$6.1875	20,225	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		600	D	\$55.62	19,625	D	
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.624	19,625	D	
Common Stock	03/02/2004		M		500	A	\$6.1875	20,125	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		500	D	\$55.626	19,625	D	
Common Stock	03/02/2004		M		2,400	A	\$6.1875	22,025	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		2,400	D	\$55.63	19,625	D	
Common Stock	03/02/2004		M		300	A	\$6.1875	19,925	D	

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	03/02/2004		S <sup>(1)</sup>		300	D	\$55.52	19,625	D	
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.522	19,625	D	
Common Stock	03/02/2004		M		400	A	\$6.1875	20,025	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		400	D	\$55.523	19,625	D	
Common Stock	03/02/2004		M		1,500	A	\$6.1875	21,125	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		1,500	D	\$55.53	19,625	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
						(A) (D)			Title Amount or Number of Shares				

**Explanation of Responses:**

I. Represents sale by William Rohn pursuant to a trading plan intended to comply with SEC rule 10b5-1.

By: Pamela A. Blas For:  
William R. Rohn

03/04/2004

\*\* Signature of Reporting  
Person

Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person*</b> <u>ROHN WILLIAM R</u>  (Last) (First) (Middle) C/O CERUS CORP 2411 STENWELL DRIVE  (Street) CONCORD CA 94520  (City) (State) (Zip)	<b>2. Issuer Name and Ticker or Trading Symbol</b> <u>BIOGEN IDEC INC [ BIIB ]</u>	<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director 10% Owner X Officer (give title below) Other (specify below) Exec VP & COO
	<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 03/02/2004	
	<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>	<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> X Form filed by One Reporting Person Form filed by More than One Reporting Person

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.531	19,625	D	
Common Stock	03/02/2004		M		1,100	A	\$6.1875	20,725	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		1,100	D	\$55.54	19,625	D	
Common Stock	03/02/2004		M		4,600	A	\$6.1875	24,225	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		4,600	D	\$55.55	19,625	D	
Common Stock	03/02/2004		M		800	A	\$6.1875	20,425	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		800	D	\$55.56	19,625	D	
Common Stock	03/02/2004		M		200	A	\$6.1875	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.57	19,625	D	
Common Stock	03/02/2004		M		700	A	\$7.7188	20,325	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		700	D	\$55.78	19,625	D	
Common Stock	03/02/2004		M		5,200	A	\$7.7188	24,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		5,200	D	\$55.79	19,625	D	
Common Stock	03/02/2004		M		5,000	A	\$7.7188	24,625	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		5,000	D	\$55.8	19,625	D	
Common Stock	03/02/2004		M		2,300	A	\$7.7188	21,925	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		2,300	D	\$55.84	19,625	D	
Common Stock	03/02/2004		M		3,700	A	\$7.7188	23,325	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		3,700	D	\$55.85	19,625	D	
Common Stock	03/02/2004		M		100	A	\$7.7188	19,725	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		100	D	\$55.856	19,625	D	
Common Stock	03/02/2004		M		400	A	\$7.7188	20,025	D	

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	03/02/2004		S <sup>(1)</sup>		400	D	\$55.862	19,625	D	
Common Stock	03/02/2004		M		200	A	\$7.7188	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.87	19,625	D	
Common Stock	03/02/2004		M		1,600	A	\$7.7188	21,225	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		1,600	D	\$55.89	19,625	D	
Common Stock	03/02/2004		M		700	A	\$7.7188	20,325	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		700	D	\$55.77	19,625	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date					
						(A) (D)			Title Amount or Number of Shares				

**Explanation of Responses:**

1. Represents sale by William Rohn pursuant to a trading plan intended to comply with SEC rule 10b5-1.

By: Pamela A. Blas For:  
William R. Rohn

03/04/2004

\*\* Signature of Reporting  
Person

Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP****OMB APPROVAL**

OMB Number: 3235-0287  
 Expires: January 31, 2008  
 Estimated average burden  
 hours per response 0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

<b>1. Name and Address of Reporting Person*</b> <b>ROHN WILLIAM R</b>  (Last) (First) (Middle) C/O CERUS CORP 2411 STENWELL DRIVE  (Street) CONCORD CA 94520  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIOGEN IDEC INC [ BIIB ]</b>  <b>3. Date of Earliest Transaction (Month/Day/Year)</b> 03/02/2004  <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director 10% Owner X Officer (give title below) Other (specify below) Exec VP & COO  <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> X Form filed by One Reporting Person Form filed by More than One Reporting Person	
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	03/02/2004		M		500	A	\$7.7188	20,125	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		500	D	\$55.76	19,625	D	
Common Stock	03/02/2004		M		200	A	\$7.7188	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.731	19,625	D	
Common Stock	03/02/2004		M		6,700	A	\$7.7188	26,325	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		6,700	D	\$55.72	19,625	D	
Common Stock	03/02/2004		M		11,500	A	\$7.7188	31,125	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		11,500	D	\$55.7	19,625	D	
Common Stock	03/02/2004		M		200	A	\$7.7188	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.71	19,625	D	
Common Stock	03/02/2004		M		200	A	\$7.7188	19,825	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		200	D	\$55.703	19,625	D	
Common Stock	03/02/2004		M		400	A	\$7.7188	20,025	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		400	D	\$55.69	19,625	D	
Common Stock	03/02/2004		M		500	A	\$7.7188	20,125	D	
Common Stock	03/02/2004		S <sup>(1)</sup>		500	D	\$55.68	19,625	D	
Common Stock								6,000	I	by Spouse
Common Stock <sup>(2)</sup>								377,388	I	by Trust

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Incentive	\$6.1875	03/02/2004		M			1,000	04/15/1999	04/14/2008	Common	1,000	(2)	72,275	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right to buy) <sup>( 2 )</sup>								( 3 )		Stock					
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	200	( 2 )	72,075	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			17,900	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	17,900	( 2 )	54,175	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			1,800	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	1,800	( 2 )	52,375	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			1,700	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	1,700	( 2 )	50,675	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	200	( 2 )	50,475	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			5,200	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	5,200	( 2 )	45,275	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			8,000	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	8,000	( 2 )	37,275	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			4,300	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	4,300	( 2 )	32,975	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	200	( 2 )	32,775	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			500	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	500	( 2 )	32,275	D	
Incentive Stock Option (right to buy) <sup>( 2 )</sup>	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	200	( 2 )	32,075	D	
Incentive Stock Option (right to	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>( 3 )</sup>	04/14/2008	Common Stock	200	( 2 )	31,875	D	



Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
buy) <sup>(2)</sup>															
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			500	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	500	<sup>(2)</sup>	31,375	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			9,800	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	9,800	<sup>(2)</sup>	21,575	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			300	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	300	<sup>(2)</sup>	21,275	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			600	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	600	<sup>(2)</sup>	20,675	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	200	<sup>(2)</sup>	20,475	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			500	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	500	<sup>(2)</sup>	19,975	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			2,400	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	2,400	<sup>(2)</sup>	17,575	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			300	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	300	<sup>(2)</sup>	17,275	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	200	<sup>(2)</sup>	17,075	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			400	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	400	<sup>(2)</sup>	16,675	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			1,500	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	1,500	<sup>(2)</sup>	15,175	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	200	<sup>(2)</sup>	14,975	D	



Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			1,100	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	1,100	<sup>(2)</sup>	13,875	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			4,600	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	4,600	<sup>(2)</sup>	9,275	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			800	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	800	<sup>(2)</sup>	8,475	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$6.1875	03/02/2004		M			200	04/15/1999 <sup>(3)</sup>	04/14/2008	Common Stock	200	<sup>(2)</sup>	8,275	D	
Incentive Stock Option (right to buy) <sup>(2)</sup>	\$7.7188	03/02/2004		M			2,200	01/01/2000 <sup>(4)</sup>	01/12/2009	Common Stock	2,200	<sup>(2)</sup>	219,875	D	

**Explanation of Responses:**

1. Represents sale by William Rohn pursuant to a trading plan intended to comply with SEC rule 10b5-1.
2. Granted under Issuer's Employee Stock Option Plan, in an exempt transaction under SEC rule 16b-3(d).
3. Option became exercisable as to 25% of the optioned shares on 4/15/99 and as to the balance of the shares in 36 equal monthly installments thereafter.
4. Option became exercisable as to 25% of the optioned shares on 1/01/2000 and as to the balance of the shares in 36 equal monthly installments thereafter.

By: Pamela A. Blas For: 03/04/2004  
William R. Rohn

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP****OMB APPROVAL**

OMB Number: 3235-0287  
 Expires: January 31, 2008  
 Estimated average burden  
 hours per response 0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person <b>ROHN WILLIAM R</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  Director 10% Owner X Officer (give title below) Other (specify below) Exec VP & COO	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 03/02/2004		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
C/O CERUS CORP 2411 STENWELL DRIVE			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	CONCORD	CA 94520				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, If any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			4,700	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	4,700	(1)	215,175	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			200	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	200	(1)	214,975	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			6,600	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	6,600	(1)	208,375	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			4,900	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	4,900	(1)	203,475	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			1,300	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	1,300	(1)	202,175	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			700	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	700	(1)	201,475	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			5,200	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	5,200	(1)	196,275	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			5,000	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	5,000	(1)	191,275	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			2,300	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	2,300	(1)	188,975	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			3,700	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	3,700	(1)	185,275	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			100	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	100	(1)	185,175	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			400	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	400	(1)	184,775	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			200	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	200	(1)	184,575	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			1,600	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	1,600	(1)	182,975	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			700	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	700	(1)	182,275	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			500	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	500	(1)	181,775	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			200	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	200	(1)	181,575	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			6,700	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	6,700	(1)	174,875	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			11,500	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	11,500	(1)	163,375	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			200	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	200	(1)	163,175	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			200	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	200	(1)	162,975	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			400	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	400	(1)	162,575	D	
Incentive Stock Option (right to buy) <sup>(1)</sup>	\$7.7188	03/02/2004		M			500	01/01/2000 <sup>(2)</sup>	01/12/2009	Common Stock	500	(1)	162,075	D	

**Explanation of Responses:**

1. Granted under Issuer's Employee Stock Option Plan, in an exempt transaction under SEC rule 16b-3(d).
2. Option became exercisable as to 25% of the optioned shares on 1/01/2000 and as to the balance of the shares in 36 equal monthly installments thereafter.

By: Pamela A. Blas For: 03/04/2004  
William R. Rohn

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person</b> <b>ROHN WILLIAM R</b>			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIOGEN IDEC INC [ BIIB ]</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director <input type="checkbox"/> 10% Owner <input type="checkbox"/> X Officer (give title below) <input type="checkbox"/> Other (specify below) <input type="checkbox"/> Chief Operating Officer	
(Last) (First) (Middle) 14 CAMBRIDGE CENTER			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 06/02/2004			
(Street) CAMBRIDGE MA 02142			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> X Form filed by One Reporting Person Form filed by More than One Reporting Person	
(City) (State) (Zip)						

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/02/2004		A		50,000	A	\$7.7188	162,075	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		900	D	\$63.13	161,175	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		100	D	\$63.15	161,075	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		300	D	\$63.17	160,775	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,000	D	\$63.18	159,775	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		500	D	\$63.19	159,275	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		400	D	\$63.2	158,875	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,800	D	\$63.21	157,075	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,000	D	\$63.22	156,075	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		200	D	\$63.25	155,875	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		200	D	\$63.26	155,675	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		8,800	D	\$63.3	146,875	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		200	D	\$63.31	146,675	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,700	D	\$63.32	144,975	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		200	D	\$63.33	144,775	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		200	D	\$63.34	144,575	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		2,900	D	\$63.35	141,675	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		200	D	\$63.36	141,475	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,200	D	\$63.38	140,275	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		5,300	D	\$63.39	134,975	D	
Common Stock	06/02/2004		S		4,200	D	\$63.4	130,775	D	
Common Stock								6,000	I	by Spouse
Common Stock								377,388	I	by Trust
Common Stock								19,625	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned**  
 (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$7.7188	06/02/2004		A		50,000	(3)	01/13/2009	Common Stock	50,000	(2)	112,075	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. Option became exercisable as to 25% of the optioned shares on 1/01/2000 and as to the balance of the shares in 36 equal monthly installments thereafter.

**Remarks:**

This is the first of two Form 4 filings which together represent the exercise and sale of an aggregate of 50,000 issuer stock options on 06/02/2004.

By: Benjamin S. Harshbarger 06/04/2004  
For: William S. Rohn

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

<b>1. Name and Address of Reporting Person</b> <b>ROHN WILLIAM R</b>			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>BIODEN IDEC INC [ BIIB ]</b>		<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) Director <input type="checkbox"/> 10% Owner <input type="checkbox"/> Officer (give title below) <input checked="" type="checkbox"/> Other (specify below) <input type="checkbox"/> Chief Operating Officer
(Last) (First) (Middle) 14 CAMBRIDGE CENTER			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> 06/02/2004		
(Street) CAMBRIDGE MA 02142			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>		
(City) (State) (Zip)			<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person		

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	06/02/2004		S <sup>(1)</sup>		1,500	D	\$63.41	129,275	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,900	D	\$63.42	127,375	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		200	D	\$63.44	127,175	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		2,000	D	\$63.45	125,175	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,400	D	\$63.47	123,775	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		300	D	\$63.5	123,475	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		600	D	\$63.56	122,875	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,800	D	\$63.7	121,075	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		400	D	\$63.71	120,675	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		100	D	\$63.76	120,575	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		100	D	\$63.78	120,475	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		3,800	D	\$63.8	116,675	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		400	D	\$63.84	116,275	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		100	D	\$63.85	116,175	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		400	D	\$63.86	115,775	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		400	D	\$63.87	115,375	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		100	D	\$63.91	115,275	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,100	D	\$63.92	114,175	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		300	D	\$63.93	113,875	D	
Common Stock	06/02/2004		S <sup>(1)</sup>		1,800	D	\$63.95	112,075	D	
Common Stock								6,000	I	by Spouse
Common Stock								377,388	I	by Trust
Common Stock								19,625	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)	5. Derivative Acquired or Disposed Of (Instr. 3, 4 and 5)	6. Amount of Derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	7. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	8. Date of Expiration (Month/Day/Year)	9. Exercisable and Vested Date (Month/Day/Year)	10. Puttable, Callable, or Convertible (Instr. 3 and 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
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				3, 4 and 5)								Reported Transaction(s) (Instr. 4)		
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares			
Stock Option (right-to-buy) (2)	\$7.7188	06/02/2004		A			50,000	(3)	01/13/2009	Common Stock	50,000	(2)	112.075	D

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans. in an exempt transaction under SEC rule 16(b)-3(d).
3. Option became exercisable as to 25% of the optioned shares on 1/01/2000 and as to the balance of the shares in 36 equal monthly installments thereafter.

**Remarks:**

This is the second of two Form 4 filings which together represent the exercise and sale of an aggregate of 50,000 issuer stock options on 06/02/2004.

By: Benjamin S. Harshbarger      06/04/2004  
 For: William S. Rohn

\*\* Signature of Reporting Person      Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>ROHN WILLIAM R</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner X Officer (give title below) Other (specify below) Chief Operating Officer	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 08/30/2004		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)						
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/30/2004		M		8,275	A	\$6.1875	8,275	D	
Common Stock	08/30/2004		S		900	D	\$58.52	7,375	D	
Common Stock	08/30/2004		S		2,100	D	\$58.53	5,275	D	
Common Stock	08/30/2004		S		3,800	D	\$58.54	1,475	D	
Common Stock	08/30/2004		S		1,475	D	\$58.55	0	D	
Common Stock	08/30/2004		M		41,125	A	\$6.9167	206,857	D	
Common Stock	08/30/2004		S		13,025	D	\$58.55	193,562	D	
Common Stock	08/30/2004		S		2,900	D	\$58.56	190,662	D	
Common Stock	08/30/2004		S		3,900	D	\$58.57	186,762	D	
Common Stock	08/30/2004		S		2,200	D	\$58.58	184,562	D	
Common Stock	08/30/2004		S		8,600	D	\$58.6	175,962	D	
Common Stock	08/30/2004		S		2,000	D	\$58.62	173,962	D	
Common Stock	08/30/2004		S		200	D	\$58.63	173,762	D	
Common Stock	08/30/2004		S		2,500	D	\$58.66	171,262	D	
Common Stock	08/30/2004		S		1,800	D	\$58.67	169,462	D	
Common Stock	08/30/2004		S		3,100	D	\$58.7	166,362	D	
Common Stock	08/30/2004		S		900	D	\$58.71	165,462	D	
Common Stock	08/30/2004		M		600	A	\$6.3125	600	D	
Common Stock	08/30/2004		S		600	D	\$58.55	0	D	
Common Stock								6,000	I	by Spouse
Common Stock								377,388	I	by Trust
Common Stock								19,625	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of	2.	3. Transaction	3A. Deemed	4. Transaction Code (Instr. 8)	5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)	7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of	9. Number of	10.	11. Nature
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Derivative Security (Instr. 3)	Conversion or Exercise Price of Derivative Security	Date (Month/Day/Year)	Execution Date, if any (Month/Day/Year)					Date Exercisable	Expiration Date	Title	Amount or Number of Shares	Derivative Security (Instr. 5)	Derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)								
Stock Option (right-to-buy) (1)	\$6.1875	08/30/2004		M			8,275	(2)	04/15/2008	Common Stock	8,275	(1)	0	D	
Stock Option (right-to-buy) (1)	\$6.9167	08/30/2004		M			41,125	(3)	02/05/2009	Common Stock	41,125	(1)	165,462	D	
Stock Option (right-to-buy) (1)	\$6.3125	08/30/2004		M			600	(4)	11/19/2007	Common Stock	600	(1)	0	D	

**Explanation of Responses:**

1. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
2. Option became exercisable as to 25% of the optioned shares on 4/15/99 and as to the balance of the shares in 36 equal monthly installments thereafter.
3. Option became exercisable as to 25% of the optioned shares on 1/01/99 and as to the balance of the shares in 36 equal monthly installments thereafter.
4. Option became exercisable as to 100% of the optioned shares on 11/19/03.

**Remarks:**

By: Benjamin S. Harshbarger 09/01/2004  
For: William R. Rohn

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person <b>ROHN WILLIAM R</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner X Officer (give title below) Other (specify below) Chief Operating Officer	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 08/30/2004		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year) 09/01/2004			
(Street)						
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/30/2004		M		8,275	A	\$6.1875	8,275	D	
Common Stock	08/30/2004		S		900	D	\$58.52	7,375	D	
Common Stock	08/30/2004		S		2,100	D	\$58.53	5,275	D	
Common Stock	08/30/2004		S		3,800	D	\$58.54	1,475	D	
Common Stock	08/30/2004		S		1,475	D	\$58.55	0	D	
Common Stock	08/30/2004		M		41,125	A	\$6.9167	206,857	D	
Common Stock	08/30/2004		S		13,025	D	\$58.55	193,562	D	
Common Stock	08/30/2004		S		2,900	D	\$58.56	190,662	D	
Common Stock	08/30/2004		S		3,900	D	\$58.57	186,762	D	
Common Stock	08/30/2004		S		2,200	D	\$58.58	184,562	D	
Common Stock	08/30/2004		S		8,600	D	\$58.6	175,962	D	
Common Stock	08/30/2004		S		2,000	D	\$58.62	173,962	D	
Common Stock	08/30/2004		S		200	D	\$58.63	173,762	D	
Common Stock	08/30/2004		S		2,500	D	\$58.66	171,262	D	
Common Stock	08/30/2004		S		1,800	D	\$58.67	169,462	D	
Common Stock	08/30/2004		S		3,100	D	\$58.7	166,362	D	
Common Stock	08/30/2004		S		900	D	\$58.71	165,462	D	
Common Stock	08/30/2004		M		600	A	\$6.3125	600	D	
Common Stock	08/30/2004		S		600	D	\$58.55	0	D	
Common Stock								6,000	I	by Spouse
Common Stock								377,388	I	by Trust
Common Stock								20,301,773.1	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)	5. Derivative Security Acquired or Disposed of (D) (Instr. 3, 4 and 5)	6. Expiration Date (Month/Day/Year)	7. Exercisable and Expirable Date (Month/Day/Year)	8. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	9. Nature of Indirect Beneficial Ownership (Instr. 4)
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			3, 4 and 5)										Reported Transaction(s) (Instr. 4)	
			Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$6.1875	08/30/2004	M			8,275	(3)	04/15/2008	Common Stock	8,275	(2)	0	D	
Stock Option (right-to-buy) (2)	\$6.9167	08/30/2004	M			41,125	(4)	02/05/2009	Common Stock	41,125	(2)	165,462	D	
Stock Option (right-to-buy) (2)	\$6.3125	08/30/2004	M			600	(5)	11/19/2007	Common Stock	600	(2)	0	D	

**Explanation of Responses:**

1. The increase in the reporting owners directly held common stock is the result of an acquisition of common stock under the Issuer's Employee Stock Purchase Plan in a transaction exempt under SEC Rule 16b-3(c).
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. Option became exercisable as to 25% of the optioned shares on 4/15/99 and as to the balance of the shares in 36 equal monthly installments thereafter.
4. Option became exercisable as to 25% of the optioned shares on 1/01/99 and as to the balance of the shares in 36 equal monthly installments thereafter.
5. Option became exercisable as to 100% of the optioned shares on 11/19/03.

**Remarks:**

By: Benjamin S. Harshbarger

09/02/2004

For: William R. Rohn

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>ROHN WILLIAM R</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  Director 10% Owner X Officer (give title below) Other (specify below) Chief Operating Officer	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 08/31/2004		6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	CAMBRIDGE MA 02142					
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	08/31/2004		M		25,000	A	\$6.9167	165,462	D	
Common Stock	08/31/2004		S		16,947	D	\$58.5	148,515	D	
Common Stock	08/31/2004		S		2,494	D	\$58.51	146,021	D	
Common Stock	08/31/2004		S		200	D	\$58.52	145,821	D	
Common Stock	08/31/2004		S		1,600	D	\$58.67	144,221	D	
Common Stock	08/31/2004		S		780	D	\$58.68	143,441	D	
Common Stock	08/31/2004		S		900	D	\$58.69	142,541	D	
Common Stock	08/31/2004		S		1,248	D	\$58.7	141,293	D	
Common Stock	08/31/2004		S		400	D	\$58.71	140,893	D	
Common Stock	08/31/2004		S		431	D	\$58.72	140,462	D	
Common Stock								6,000	I	by Spouse
Common Stock								377,388	I	by Trust
Common Stock								20,301,7731	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V		Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (1)	\$6.9167	08/31/2004		M		25,000	(2)	02/05/2008	Common Stock	25,000	(1)	140,462	D	

**Explanation of Responses:**

1. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).  
2. Option became exercisable as to 25% of the optioned shares on 1/01/99 and as to the balance of the shares in 36 equal monthly installments thereafter.

**Remarks:**

By: Benjamin S. Harshbarger 09/02/2004  
For: William R. Rohn  
\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

**OMB APPROVAL**

OMB Number: 3235-0287  
Expires: January 31, 2008  
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person <b>ROHN WILLIAM R</b>			2. Issuer Name and Ticker or Trading Symbol <b>BIOGEN IDEC INC [ BIIB ]</b>		5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) Chief Operating Officer	
(Last)	(First)	(Middle)	3. Date of Earliest Transaction (Month/Day/Year) 11/17/2004		6. Individual or Joint/Group Filing (Check Applicable Line)  <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person	
14 CAMBRIDGE CENTER			4. If Amendment, Date of Original Filed (Month/Day/Year)			
(Street)	(State)	(Zip)				
CAMBRIDGE	MA	02142				
(City)	(State)	(Zip)				

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	11/17/2004		M		75,000	A	\$6.9167	140,462	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		300	D	\$57.91	139,862	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		500	D	\$57.92	139,362	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		1,900	D	\$57.93	137,462	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		1,200	D	\$57.94	136,262	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		2,100	D	\$57.97	134,162	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		2,000	D	\$58	132,162	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		2,600	D	\$58.01	129,562	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		1,900	D	\$58.02	127,662	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		3,000	D	\$58.03	124,662	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		100	D	\$58.04	124,562	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		6,700	D	\$58.05	117,862	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		2,100	D	\$58.06	115,762	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		2,700	D	\$58.07	113,062	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		2,000	D	\$58.08	111,062	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		5,100	D	\$58.09	105,962	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		6,300	D	\$58.1	99,662	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		1,400	D	\$58.11	98,262	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		1,500	D	\$58.12	96,762	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		100	D	\$58.13	96,662	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		300	D	\$58.15	96,662	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		14,300	D	\$58.16	82,362	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		5,400	D	\$58.17	76,962	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		1,800	D	\$58.18	75,162	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		2,000	D	\$58.19	73,162	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		4,800	D	\$58.2	68,362	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		200	D	\$58.21	68,162	D	

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			Code	V	Amount	(A) or (D)	Price				
Common Stock								6,000	I	by Spouse	
Common Stock								377,388	I	by Trust	
Common Stock								20,301,7731	D		

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)															
1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, If any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Stock Option (right-to-buy) (2)	\$6.9167	11/17/2004		M			75,000	(3)	02/05/2008	Common Stock	75,000	(2)	65,462	D	

**Explanation of Responses:**

1. Sale pursuant to a trading plan intended to comply with Rule 10b5-1 of the Securities Exchange Act of 1934.
2. Granted under one of the Issuer's stock option plans, in an exempt transaction under SEC rule 16(b)-3(d).
3. Option became exercisable as to 25% of the optioned shares on 1/01/99 and as to the balance of the shares in 36 equal monthly installments thereafter.

**Remarks:**

This is the first of two Form 4 filings which together represent the exercise of an aggregate of 75,000 Issuer options on 11/17/2004.

By: Benjamin S. Harshbarger  
 For: William R. Rohn 11/19/2004

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

**FORM 4****UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

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			Code	V	Amount	(A) or (D)	Price			
Common Stock	11/17/2004		S <sup>(1)</sup>		1,700	D	\$58.29	66,462	D	
Common Stock	11/17/2004		S <sup>(1)</sup>		1,000	D	\$58.3	65,462	D	
Common Stock								6,000	I	by Spouse
Common Stock								377,388	I	by Trust
Common Stock								20,301,7731	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

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Stock Option (right-to-buy) <sup>(2)</sup>	\$6.9167	11/17/2004		M			75,000	<sup>(3)</sup>	02/05/2008	Common Stock	75,000	<sup>(2)</sup>	65,462	D	

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